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ON AGE DEPENDENT BRANCHING PROCESSES

by

Howard Weiner

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INTRODUCTION

This paper deals with asymptotic properties of various models of age-dependent branching processes, relying heavily on Harris [3].

Part I considers cell growth in which a cell proceeds in a sequential manner through n independent states, state R with its life distribution F_R , $R=1,2,\dots,n$. At the end of mitosis, the n^{th} state, the cell divides into similar cells, the number of which is governed by a generating function h , independent of the time and other cells of the process.

Let $Z(t)$ be the number of cells at t , and $Z_R(t)$, $R=1,2,\dots,n$, be the number of cells in state R at t . For increasing cell populations, that is, $h'(1) \equiv m > 1$, we treat the following topics, ($t \rightarrow \infty$ throughout).

- (1) $E[Z(t)]$ and $\text{Var}[Z(t)]$
- (2) forward, backward, and total times: Given that a cell is in the R^{th} state at t , to find
 - (a) the distribution of its time to reach the end of that state,
 - (b) the distribution of the time since it entered that state, and
 - (c) the total time it will have spent in that state, respectively.
- (3) asymptotic fraction of cells in state $R \equiv P_R$ and the relation between P_R and $E[Z_R(t)]$.

A variation of the above model treats cell growth in which the cell proceeds from state to state according to a general semi-Markov process until the mitotic state is completed, when division into similar cells in accord with h occurs.

We treat the 3 state semi-Markov case in detail to obtain

- (1) the equivalent life distribution G of a cell,
- (2) asymptotic fraction of cells in a state,
- (3) forward, backward, and total times in a state.

For the general n -state semi-Markov case, expressions for (2) and (3) above are found, and it is shown that as $h'(1) \equiv m \downarrow 1$, that the asymptotic fraction of cells in a state approaches a simple limiting form which agrees with a result of Smith [3].

For both the sequence of states and general semi-Markov model, the convergence of

$$W_R(t) \equiv \frac{Z_R(t)}{E[Z_R(t)]} \rightarrow W_R, \quad R=1,2,\dots,n,$$

a non-degenerate random variable, in quadratic mean is discussed.

The correlations

$$\lim_{t \rightarrow \infty} \rho(W_R(t), W_S(t)) = \rho(W_R, W_S) = 1,$$

$R, S = 1, 2, \dots, n$, and $W_R = W_S$ a.e. Moments of $W \equiv W_R$ may be easily obtained.

Part II considers the random variable $N(t) \equiv$ the total number of births by t in a simple age dependent branching process for $m > 1$. The following topics are treated for t large:

(1) $E[N(t)]$ and $\text{Var}[N(t)]$

(2) $W_0(t) \equiv \frac{N(t)}{E[N(t)]} \rightarrow W_0$, a non-degenerate random variable, in

quadratic mean.

(3) Let $Z(t)$ = number of cells at t .

From [3],

$$W_1(t) = \frac{Z(t)}{E[Z(t)]} \rightarrow W_1 \text{ in quadratic mean.}$$

It is shown that the correlations satisfy

$$\lim_{t \rightarrow \infty} \rho(W_0(t), W_1(t)) = \rho(W_0, W_1) = 1$$

and that $W_0 = W_1$ a.e.

(4) The results for $E[N(t)]$ are checked with the corresponding discrete case by matrix methods.

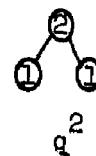
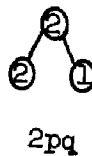
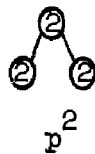
(5) For the case $m < 1$, $N(t) \rightarrow N_0$ a.e. Moments of N_0 may be calculated.

(6) For $m=1$ and $m < 1$, moments of $N(t)$ are discussed for both discrete and continuous time.

Part III treats the case of two types of cells, of which only one type may divide while the other either accumulates or is eventually absorbed in the medium. An example of this is the production of stem cells and red blood cells from parent stem cells. Two related models are considered, both examples of the "reducible case". For an outline of the irreducible case, see Snow [8]. Increasing cell populations are considered.

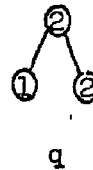
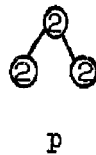
A binary fission case of each model may be represented schematically to indicate the various combinations of cell births with corresponding probabilities, where type 2 represents the proliferating, and type 1 the non-proliferating cell.

Model I



where $p + q = 1$.

Model II



where $p + q = 1$.

Let $Z_i(t)$ = number of cells of type i at t , $i=1,2$.

$N_i(t)$ = total number of births of type i by t .

The following topics are treated for t large:

- (1) means and second moments of $Z_i(t)$, $N_i(t)$, $i=1,2$.
- (2) Results for the means in (1) are compared with the discrete case by matrix methods, and a comparison is made with results of Snow [8].

$$(3) \quad W_1(t) \equiv \frac{Z_1(t)}{E[Z_1(t)]} \rightarrow W_1 \quad \text{in quadratic mean, } i=1,2$$

$$W_{01}(t) \equiv \frac{N_1(t)}{E[N_1(t)]} \rightarrow W_{01} \quad \text{in quadratic mean, } i=1,2,$$

(4) The limits of the pairwise correlations, as $t \rightarrow \infty$, of $W_1(t)$, $W_2(t)$, $W_{01}(t)$, $W_{02}(t)$ are respectively equal to the corresponding pairwise correlations among W_1 , W_2 , W_{01} , W_{02} , and are all equal to 1, and $W_1 = W_2 = W_{01} = W_{02}$ a.e.

PART I - MULTI-STATE CELLS

1.1 Sequence of States.

A cell exhibits growth and division into other cells according to the scheme to be described.

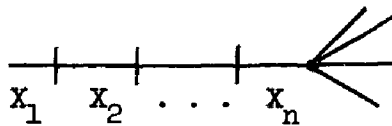
The cell enters state 1, for which it remains a time which is a random variable X_1 with distribution function F_1 , then proceeds to state 2, with distribution function F_2 , and so on until it completes the n^{th} state of growth, the mitotic state, after which it divides. The overall life distribution of the cell is

$$G = F_1 * F_2 * \dots * F_n .$$

The cell divides into k other cells with probability p_k , $k=0,1,2,\dots$ each with independent, identically distributed growth pattern as the parent cell, and independent of each other.

Define
$$h(s) = \sum_{k=0}^{\infty} p_k s^k .$$

Schematically:



A brief treatment of the two-state case is given in [3], Ch. 6, sect. 26, where a formula for the limiting mitotic index, which is the limiting fraction of cells in mitosis, is given.

As an example, certain normally proliferating cells pass through four states to division, called the G_1 , S, G_2 , and mitotic state in that order. Each corresponds to a certain condition of the cell and has

a certain sensitivity to radiation. For example, the S state is the DNA synthesizing state, and it along with the mitotic state is more sensitive to radiation than either the G_1 or G_2 which are called resting states. The results of this paper, especially part I may aid in the computation of the fraction of cells heavily damaged by radiation. See Stohlman [9].

1.2 $E[Z(t)]$, $Var[Z(t)]$.

To discuss cell behavior, it is convenient to introduce the generating function of cell life.

Definition. Let $Z(t)$ denote the number of cells at time t , starting with one cell at $t = 0$.

Definition. $F(s, t) = \sum_{k=0}^{\infty} P[Z(t) = k] s^k$.

We have [3] (Ch. 6, sect. 7) the relation

$$F(s, t) = s(1-G(t)) + \int_0^t h(F(s, t-u)) dG(u)$$

$$m(t) \equiv E[Z(t)] = \left. \frac{\partial F(s, t)}{\partial s} \right|_{s=1}$$

$$m(t) = 1-G(t) + m \int_0^t m(t-u) dG(u) .$$

We assume $m \equiv h'(1) > 1$, $h''(1) < \infty$. Define $\alpha > 0$ by the equation $\int_0^{\infty} e^{-\alpha u} dG(u) = \frac{1}{m}$. By lemma 1 of the appendix, as $t \rightarrow \infty$,

$$m(t) \sim \left[\frac{\int_0^{\infty} e^{-\alpha u} [1-G(u)] du}{m \int_0^t u e^{-\alpha u} dG(u)} \right] e^{\alpha t}$$

or

$$m(t) \sim \left[\frac{m-1}{\alpha m^2 \int_0^\infty u e^{-\alpha u} dG(u)} \right] e^{\alpha t} = n_0 e^{\alpha t}.$$

A further result has ([3] Ch. 6, sect. 19) for $t \rightarrow \infty$,

$$Z(t) \sim W n_0 e^{\alpha t}$$

where W is a random variable such that

$$\sigma^2(W) = \frac{(m+h''(1)) \int_0^\infty e^{-2\alpha u} dG(u) - 1}{1-m \int_0^\infty e^{-2\alpha u} dG(u)}.$$

To find $\text{Var}[Z(t)]$, note

$$\text{Var}[Z(t)] = \frac{\partial^2 F(s, t)}{\partial s^2} \Big|_{s=1} - m^2(t)$$

and using theorem 18.1 of [3], Ch. 6, we obtain, as might be expected,

$$\text{Var } Z(t) \sim \sigma^2(W) n_0^2 e^{2\alpha t}.$$

1.3 Forward, backward and total times.

1.3a Total cell.

The total backward time is the distribution of time the cell has been living until t , given that it is alive at the present time t . Let $A(x)$ = distribution function of the backward time. Then ([3], Ch. 6, sect. 24)

$$A(x) = \frac{\int_0^x e^{-\alpha t} [1-G(t)] dt}{\int_0^{\infty} e^{-\alpha t} [1-G(t)] dt}.$$

We may find the forward time distribution, denoted by $B(x)$, for the total cell by using $A(x)$.

Let

$$P_B(t, x) = P [\text{cell will die by age } t+x | \text{age is now } t]$$

$$P_B(t, x) = \frac{G(t+x) - G(t)}{1-G(t)}.$$

We then have

$$B(x) = \int_0^{\infty} P_B(t, x) dA(t) = \frac{\int_0^{\infty} e^{-\alpha t} [G(t+x) - G(t)] dt}{\int_0^{\infty} e^{-\alpha t} [1-G(t)] dt}.$$

Denote the total time distribution for the entire cell life by $C(x)$.

$$P_C(t, x) = P[\text{cell will die by age } x | \text{age is now } t].$$

$$P_C(t, x) = \frac{G(x) - G(t)}{1-G(t)}, \quad x \geq t; \quad P_C(t, x) = 0, \quad t > x.$$

$$C(x) = \int_0^{\infty} P_C(t, x) dA(t) = \frac{\int_0^x e^{-\alpha t} [G(x) - G(t)] dt}{\int_0^{\infty} e^{-\alpha t} [1-G(t)] dt}.$$

Note $A(x) * B(x) \neq C(x)$.

1.3b Each state.

Given that the cell proceeds sequentially through n states before mitosis, with corresponding distribution functions F_1, F_2, \dots, F_n .

As before, $G = F_1 * F_2 * \dots * F_n$ and α is such that

$$\int_0^{\infty} e^{-\alpha u} dG(u) = \frac{1}{m}.$$

To find $A_1(x)$, the backward time in state 1, we proceed as in Theorem 24.1 of [3], Ch. 6.

Denote $Z_1(t)$ = the number of cells at t in state 1.

$Z_1(t, x)$ = the number of cells at t in state 1 whose age is $\leq x$. Then if $F_1(s, t) = \sum_{j=0}^{\infty} P[Z_1(t) = j] s^j$

$$F_1(s, x, t) = \sum_{j=0}^{\infty} P[Z_1(t, x) = j] s^j$$

we obtain

$$F_1(s, t) = [1 - F_1(t)]s + F_1(t) - G(t) + \int_0^t h(F_1(s, t-u)) dG(u)$$

and

$$E[Z_1(t)] \equiv m_1(t) = 1 - F_1(t) + m \int_0^t m_1(t-u) dG(u)$$

$$\begin{aligned} F_1(s, x, t) &= [1 - F_1(t)](sJ(x-t) + 1 - J(x-t)) + F_1(t) - G(t) \\ &\quad + \int_0^t h(F_1(s, x, t-u)) dG(u) \end{aligned}$$

$$\text{where } J(r) = \begin{cases} 1, & r \geq 0 \\ 0, & r < 0 \end{cases}$$

$$E[Z_1(t, x)] \equiv m_1(t, x) = [1 - F_1(t)] J(x-t) + m \int_0^t m_1(x, t-u) dG(u).$$

Solving for $m_1(t, x)$ and $m_1(t)$ for t large by lemma 1 of the appendix,

$$\frac{m_1(t, x)}{m_1(t)} \sim A_1(x) = \frac{\int_0^x e^{-\alpha t} [1 - F_1(t)] dt}{\int_0^\infty e^{-\alpha t} [1 - F_1(t)] dt}.$$

To find $B_1(x)$, the forward time in state 1, we use $A_1(x)$ as done before.

Let $P_{1B}(t, x) = P[\text{cell will leave state 1 by age } t+x | \text{age in state 1 is } t]$

$$P_{1B}(t, x) = \frac{F_1(t+x) - F_1(t)}{1 - F_1(t)}.$$

$$B_1(x) = \int_0^\infty P_{1B}(t, x) dA_1(t) = \frac{\int_0^\infty e^{-\alpha t} [F_1(t+x) - F_1(t)] dt}{\int_0^\infty e^{-\alpha t} [1 - F_1(t)] dt}.$$

To obtain $C_1(x)$, the "total time" in state 1, define

$P_{1C}(t, x) = P[\text{cell will leave state 1 by age } x | \text{age in state 1 is } t].$

$$P_{1C}(t, x) = \frac{F_1(x) - F_1(t)}{1 - F_1(t)}, \quad x \geq t \quad \text{and} \quad P_{1C}(t, x) = 0, \quad x < t$$

$$C_1(x) = \int_0^\infty P_{1C}(t, x) dA_1(t) = \frac{\int_0^x e^{-\alpha t} [F_1(x) - F_1(t)] dt}{\int_0^\infty e^{-\alpha t} [1 - F_1(t)] dt}.$$

Let $A_2(x)$ be the backward time in state 2.

Denote by $Z_2(t, x)$ the number of cells in state 2 at time t whose age is $\leq x$.

Since

$$P[X_1 + X_2 \geq t; t > X_1 \geq t-x] = \int_{t-x}^t dF_1(x_1) \int_{t-x_1}^{\infty} dF_2(x_2)$$

and

$$P[X_1 + X_2 \geq t; t > X_1] = F_1(t) - F_1 * F_2(t),$$

defining

$$F_2(s, t) = \sum_{j=0}^{\infty} P[Z_2(t) = j] s^j$$

$$F_2(s, x, t) = \sum_{j=0}^{\infty} P[Z_2(t, x) = j] s^j$$

we obtain

$$\begin{aligned} F_2(s, t) &= s[F_1(t) - F_1 * F_2(t)] + 1 - G(t) - [F_1(t) - F_1 * F_2(t)] \\ &\quad + \int_0^t h(F_2(s, t-u)) dG(u) \end{aligned}$$

and

$$\begin{aligned} F_2(s, x, t) &= s \left[\int_{t-x}^t dF_1(x_1) \int_{t-x_1}^{\infty} dF_2(x_2) \right] + 1 - G(t) - \left[\int_{t-x}^t dF_1(x_1) \int_{t-x_1}^{\infty} dF_2(x_2) \right] \\ &\quad + \int_0^t h(F_2(s, x, t-u)) dG(u) \end{aligned}$$

$$m_2(t) \equiv E[Z_2(t)] = \left. \frac{\partial F_2(s, t)}{\partial s} \right|_{s=1}$$

$$m_2(t, x) \equiv E[Z_2(t, x)] = \left. \frac{\partial F_2(s, x, t)}{\partial s} \right|_{s=1}.$$

Using lemma 1 of the appendix, for $t \rightarrow \infty$, we find that

$$\frac{m_2(t, x)}{m_2(t)} \sim A_2(x) = \frac{\int_0^x e^{-\alpha t} [F_1(t) - F_1 * F_2(t)] dt + \int_x^\infty e^{-\alpha t} \left[\int_{t-x}^t dF_1(x_1) \int_{t-x_1}^\infty dF_2(x_2) \right] dt}{\int_0^\infty e^{-\alpha t} [F_1(t) - F_1 * F_2(t)] dt}.$$

To obtain $B_2(x)$, the forward time in state 2, define

$$P_{2B}(t, x) = P[t+x > X_1 + X_2 \geq t ; X_1 < t]$$

$$P_{2B}(t, x) = \int_0^t dF_1(x_1) \int_{t-x_1}^{t+x-x_1} dF_2(x_2).$$

Then

$$B_2(x) = \int_0^\infty P_{2B}(t, x) dA_2(t) = \frac{\int_0^\infty e^{-\alpha t} \left[\int_0^t dF_1(x_1) \int_{t-x_1}^{t+x-x_1} dF_2(x_2) \right] dt}{\int_0^\infty e^{-\alpha t} [F_1(t) - F_1 * F_2(t)] dt}.$$

Similarly, for $C_2(x)$, the total time in state 2, define

$$P_{2C}(t, x) = P[x > X_1 + X_2 \geq t ; X_1 < t], \quad x \geq t ; \quad P_{2C}(t, x) = 0, \quad t > x.$$

$$P_{2C}(t, x) = \int_0^t dF_1(x_1) \int_{t-x_1}^{x-x_1} dF_2(x_2), \quad x \geq t ; \quad P_{2C}(t, x) = 0, \quad t > x$$

$$C_2(x) = \int_0^\infty P_{2C}(t, x) dA_2(t) = \frac{\int_0^x e^{-\alpha t} \left[\int_0^t dF_1(x_1) \int_{t-x_1}^{x-x_1} dF_2(x_2) \right] dt}{\int_0^\infty e^{-\alpha t} [F_1(t) - F_1 * F_2(t)] dt}.$$

In general, to find $A_k(x)$, $B_k(x)$, and $C_k(x)$, $k \geq 2$, define $G_k(x) = F_1 * F_2 * \dots * F_k(x)$, then we use the same arguments as for $A_2(x)$, $B_2(x)$, $C_2(x)$, where G_{k-1} corresponds to F_1 and F_k to F_2 . Thus we obtain, for $k \geq 2$

$$A_k(x) = \frac{\int_0^x e^{-\alpha t} [G_{k-1}(t) - G_k(t)] dt + \int_x^\infty e^{-\alpha t} \left[\int_{t-x}^t dG_{k-1}(x_1) \int_{t-x_1}^\infty dF_k(x_2) \right] dt}{\int_0^\infty e^{-\alpha t} [G_{k-1}(t) - G_k(t)] dt}$$

$$B_k(x) = \frac{\int_0^\infty e^{-\alpha t} \left[\int_0^t dG_{k-1}(x_1) \int_{t-x_1}^{t+x-x_1} dF_k(x_2) \right] dt}{\int_0^\infty e^{-\alpha t} [G_{k-1}(t) - G_k(t)] dt}$$

$$C_k(x) = \frac{\int_0^x e^{-\alpha t} \left[\int_0^t dG_{k-1}(x_1) \int_{t-x_1}^{x-x_1} dF_k(x_2) \right] dt}{\int_0^\infty e^{-\alpha t} [G_{k-1}(t) - G_k(t)] dt}.$$

It is easily shown that all of the above distributions may be derived solely by means of generating functions following theorem 24.1 of ([3], Ch. 6), as was done above in obtaining $A_1(x)$ and $A_2(x)$.

Further, it is again possible to derive all of the above distributions very quickly by heuristic arguments similar to one due to R.A. Fisher. See ([3], Ch. 6, sect. 24).

1.4 Asymptotic fraction of cells in each state.

As before, we consider cell growth through a sequence of states as defined above, making the same assumptions and using the same notation.

Definition: $P_R(y) = P[\text{cell of age } y \text{ is in state } R], R=1,2,\dots,n.$

Definition: $P_R = \text{asymptotic fraction of cells in state } R.$

For the case $n = 2$, P_2 is obtained in [3], Ch. 6, sect. 26. In general, P_n is called the mitotic index. We have

$$P_R(y) = P\left[\sum_{i=1}^{R-1} X_i < y; \sum_{i=1}^R X_i \geq y \mid \sum_{i=1}^n X_i \geq y\right].$$

As before, denoting $G_k(x) = F_1 * F_2 * \dots * F_k(x)$ and $G(x) = F_1 * F_2 * \dots * F_n$ we may write

$$P_R(y) = \frac{G_{R-1}(y) - G_R(y)}{1-G(y)}$$

$$P_R = \int_0^\infty P_R(y) dA(y) = \frac{\alpha m}{m-1} \int_0^\infty [G_{R-1}(y) - G_R(y)] e^{-\alpha y} dy$$

1.5 $E[Z_R(t)]$, $\text{Var}[Z_R(t)]$.

We now obtain the asymptotic mean and variance of the number of cells in each state.

Let $Z_R(t) = \text{number of cells in state } R \text{ at } t.$

Define $F_R(s,t) = \sum_{j=0}^{\infty} P[Z_R(t) = j] s^j.$

By the arguments in the previous section, we obtain

$$\begin{aligned} F_R(s,t) &= s[G_{R-1}(t) - G_R(t)] + 1 - G(t) - [G_{R-1}(t) - G_R(t)] \\ &\quad + \int_0^t h(F_R(s,t-u)) dG(u). \end{aligned}$$

From $m_R(t) \equiv E[Z_R(t)] = \frac{\partial F_R(s, t)}{\partial s} \Big|_{s=1}$, and using lemma 1 of appendix 2 for t large,

$$m_R(t) \sim \left[\frac{\int_0^\infty e^{-\alpha t} [G_{R-1}(t) - G_R(t)] dt}{m \int_0^\infty t e^{-\alpha t} dG(t)} \right] e^{\alpha t} = n_R e^{\alpha t} .$$

Also, since $\text{Var}[Z_R(t)] = \frac{\partial^2 F_R(s, t)}{\partial s^2} \Big|_{s=1} - [m_R(t)]^2$, for t large, using the method of lemma 18.1 of [3], Ch. 6, we obtain

$$\text{Var}[Z_R(t)] \sim n_R^2 \left[\frac{(h''(1) + m) \int_0^\infty e^{-2\alpha u} dG(u) - 1}{1 - m \int_0^\infty e^{-2\alpha u} dG(u)} \right] e^{2\alpha t} .$$

As noted in [3], Ch. 6, sect. 18, the denominator is positive since

$$\int_0^\infty e^{-2\alpha t} dG(t) < \int_0^\infty e^{-\alpha t} dG(t) = \frac{1}{m} .$$

From the first section of this paper,

$$E[Z(t)] \equiv m(t) = \left[\frac{m-1}{\alpha m^2 \int_0^\infty u e^{-\alpha u} dG(u)} \right] e^{\alpha t} .$$

Hence, as we may have expected, for t large,

$$\frac{m_R(t)}{m(t)} \sim P_R .$$

The above quantities are of little practical interest in the cases $m=1$ and $m < 1$, since it is known that the populations die out with probability one in those cases. See [3], Ch. 6, sects. 1-14.

1.6 Cell growth by states according to a semi-Markov process.

We consider the following model. A cell evolves via states to mitosis, but instead of proceeding sequentially from one intermediate state to the next in a deterministic way, instead the state selection proceeds according to a Markov chain. Specifically, given n states, including the mitotic state (denoted by the n^{th} state), assume there exists an $n \times n$ irreducible positive recurrent transition probability matrix P , with zero trace, giving the probabilities of transition from one state to the next during the growth of a cell. As soon as the n^{th} , or mitotic state, is completed, the cell divides into r cells with probability P_r , $r=0,1,2,\dots$ each with a growth pattern independent and identically distributed as the parent cell, and independent of each other. Define

$$h(s) = \sum_{r=0}^{\infty} P_r s^r, \quad h'(1) \equiv \pi > 1.$$

The time spent in the k^{th} state, $k=1,2,\dots,n$ given that the next transition is into state j , for $j=1,2,\dots,n$ and $k \neq j$, is a random variable X_{kj} with non-lattice distribution function F_{kj} , $F_{kj}(0) = 0$, dependent on the k^{th} and j^{th} states, but otherwise independent of the state of the system.

At present, there appears to be no physical example of this process in cell growth, but a possible interpretation is that a cell which

evolves from state to state selects the most "accessible" state at each transition, where "accessibility" may be considered to be determined in accord with a Markov process.

We begin with a study of the 3-state semi-Markov model. For this case we compute the equivalent life distribution $G(t)$ of the cell, the forward, backward, and total time distributions for a particular state, and the asymptotic probability of a cell being in a given state [asymptotic fraction of the culture in a given state]. Further, we let $m \downarrow 1$, or equivalently, $\alpha \downarrow 0$, for α defined by

$$\int_0^{\infty} e^{-\alpha u} dG(u) = \frac{1}{m},$$

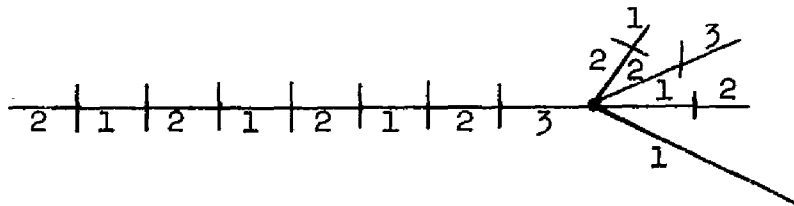
and compare our results with those of Smith [7].

To generalize, for the case of n states, we compute the asymptotic fraction of cells in a given state as $\alpha \downarrow 0$, and again compare with Smith [7].

1.7 Three state semi-Markov model.

Let
$$P = \begin{pmatrix} o & a & b \\ c & o & d \\ p & q & o \end{pmatrix}, \quad \begin{aligned} a+b &= c+d = p+q = 1 \\ a,b,c,d,p,q &> 0 \end{aligned}$$

Schematically,



State "3" is the mitotic state in the figure. Define

$$\phi_{kj}(t) = \int_0^\infty e^{-ty} dF_{kj}(y) \quad \begin{matrix} k=1,2,3 \\ j=1,2,3 \text{ and } j \neq k. \end{matrix}$$

1.7a Equivalent life.

A consideration of the various ways in which a cell may progress through the mitotic state yields the following Laplace-Stieltjes transform for the equivalent life distribution G .

$$\phi_G = (pb \phi_{13} + pda \phi_{12}\phi_{23} + qcb \phi_{21}\phi_{13} + qd \phi_{23})(p \phi_{31} + q \phi_{32}) \sum_{n=0}^{\infty} (ac \phi_{21}\phi_{12})^n$$

or

$$\phi_G = \frac{(pb \phi_{13} + pda \phi_{12}\phi_{23} + qcb \phi_{21}\phi_{13} + qd \phi_{23})(p \phi_{31} + q \phi_{32})}{1 - ac \phi_{21}\phi_{12}}$$

1.7b Fraction of cells per state, P_R .

Let

P_1 = asymptotic fraction of cells in state 1

$q_1(y) = P[\text{cell in state 1 at age } y].$

Since the equivalent age distribution of the cell, $A(x)$, is

$$A(x) = \frac{\int_0^x e^{-\alpha t} [1-G(t)] dt}{\int_0^\infty e^{-\alpha t} [1-G(t)] dt},$$

we see that ([3], Ch. 6, sect. 2C)

$$P_1 = \frac{\int_0^\infty q_1(y) e^{-\alpha y} dy}{\int_0^\infty [1-G(y)] e^{-\alpha y} dy}$$

where $\alpha > 0$ is defined by

$$\int_0^{\infty} e^{-\alpha y} dG(y) = \frac{1}{m}.$$

To compute $q_1(y)$, write

$$\begin{aligned} q_1(y) &= pP[\text{cell in state 1 at age } y | \text{cell born into state 1}] \\ &\quad + qP[\text{cell in state 1 at age } y | \text{cell born into state 2}], \end{aligned}$$

so that

$$\begin{aligned} q_1(y) &= p \sum_{n=0}^{\infty} (ac)^n [F_{12} * F_{21}]^{(n)}(y) - (F_{12} * F_{21})^{(n)} * (aF_{12} + bF_{13})(y)] \\ &\quad + qc \sum_{n=0}^{\infty} (ac)^n [(F_{12} * F_{21})^{(n)} * F_{21}(y) - (F_{12} * F_{21})^{(n)} * F_{21} * (aF_{12} + bF_{13})(y)] \end{aligned}$$

where $F_{ij}^{(n)}$ is the n^{th} convolution of F_{ij} , $i=1,2$, and $j=1,2$, $j \neq i$,
and

$$F_{ij}^{(0)}(\xi) = U(\xi) = \begin{cases} 1 & \xi \geq 0 \\ 0 & \xi < 0 \end{cases}.$$

We have

$$\int_0^{\infty} q_1(y) e^{-\alpha y} dy = \frac{\phi_{q_1}(\alpha)}{\alpha}$$

where $\phi_{q_1}(\alpha) = \int_0^{\infty} e^{-\alpha y} dq_1(y)$, the Laplace-Stieltjes transform of $q_1(y)$ evaluated at α .

Taking Laplace-Stieltjes transforms evaluated at α , using the previous expression for $q_1(y)$,

$$\begin{aligned}\phi_{q_1}(\alpha) &= p \sum_{n=0}^{\infty} (ac)^n (\phi_{12}\phi_{21})^n [1-(a\phi_{12}+b\phi_{13})](\alpha) \\ &+ qc \sum_{n=0}^{\infty} (ac)^n \phi_{21} (\phi_{12}\phi_{21})^n [1-(a\phi_{12}+b\phi_{13})](\alpha).\end{aligned}$$

$$\frac{\phi_{q_1}(\alpha)}{\alpha} = \left[\frac{1-(a\phi_{12}+b\phi_{13})(\alpha)}{\alpha} \right] \left[\frac{p + qc \phi_{21}(\alpha)}{1-ac \phi_{12}(\alpha)\phi_{21}(\alpha)} \right].$$

Since

$$\begin{aligned}\frac{1-\phi_G(\alpha)}{\alpha} &= \int_0^{\infty} [1-G(y)] e^{-\alpha y} dy = \frac{1}{\alpha} [1 - \frac{1}{m}] \\ P_1 &= \frac{\frac{\phi_{q_1}(\alpha)}{\alpha}}{\frac{1-\phi_G(\alpha)}{\alpha}} = \frac{\left[\frac{1-(a\phi_{12}+b\phi_{13})(\alpha)}{\alpha} \right] \left[\frac{p + qc \phi_{21}(\alpha)}{1-ac \phi_{12}(\alpha)\phi_{21}(\alpha)} \right]}{\frac{1}{\alpha} [1 - \frac{1}{m}]}\end{aligned}$$

For comparison with r_1 to be defined, we express ϕ_G in terms of ϕ_{ij} , $i=1,2,3$, $j=1,2,3$, $i \neq j$. Then

$$P_1 = \frac{\left[\frac{1-(a\phi_{12}+b\phi_{13})(\alpha)}{\alpha} \right] [p + qc \phi_{21}(\alpha)]}{1-ac\phi_{12}(\alpha)\phi_{21}(\alpha) - (pb\phi_{13}(\alpha) + pda\phi_{12}(\alpha)\phi_{23}(\alpha) + qcb\phi_{21}(\alpha)\phi_{13}(\alpha) + qd\phi_{23}(\alpha)) (p\phi_{31}(\alpha) + q\phi_{32}(\alpha))}$$

1.7c Comparison with a result of Smith.

To compare this with a result by Smith [7], we compute

$$r_1 = \frac{\int_0^{\infty} [1-(aF_{12}(y)+bF_{13}(y))] e^{-\alpha y} dy}{\int_0^{\infty} [1-R_1(y)] e^{-\alpha y} dy}$$

where $R_1(y)$ is the recurrence time distribution of the event:
[cell branch enters state 1]. That is, we follow any cell branch, or
strand, until state 1 is re-entered for the first time in order to
compute R_1 . We mention that an unsolved problem is to follow all cell
branches until state 1 is re-entered for the first time among all
branches, and to compute a recurrence time distribution $\tilde{R}(y)$ for this
case.

$$r_1 = \frac{\frac{1-(a\phi_{12}+b\phi_{13})(\alpha)}{\alpha}}{\frac{1-\phi_{R_1}(\alpha)}{\alpha}}$$

where

$$\phi_{R_1} = \frac{ac\phi_{12}\phi_{21} + adp\phi_{12}\phi_{23}\phi_{31} + bq\phi_{13}\phi_{32}\phi_{21} + bp\phi_{13}\phi_{31}}{1-qd\phi_{23}\phi_{32}}$$

$$r_1 = \frac{\frac{1-(a\phi_{12}+b\phi_{13})(\alpha)}{\alpha}}{\frac{1-qd\phi_{23}\phi_{32}-(ac\phi_{12}\phi_{21}+adp\phi_{12}\phi_{23}\phi_{31}+bq\phi_{13}\phi_{32}\phi_{21}+bp\phi_{13}\phi_{31})(\alpha)}{\alpha(1-qd\phi_{23}\phi_{32})}}$$

In general, for $\alpha > 0$, $P_1 \neq r_1$, and this definition of recur-
rence time distribution R , Smith's theorem 5 [7] can not be extended
to this semi-Markov process in this way.

We may let $\alpha \downarrow 0$ in the expressions for P_1 and r_1 .

Setting $\alpha = 0$, we see that

$$P_1 = r_1 ,$$

yielding Smith's result in the limit as $m \downarrow 1$. Further, for the case $\alpha = 0$,

$$P_1 = \frac{\int_0^\infty q_1(y) dy}{\int_0^\infty [1-G(y)] dy} = \frac{(\frac{p+qc}{1-ac})\mu_1}{\int_0^\infty u dG(u)} = \frac{\frac{\pi_1}{\pi_3} \mu_1}{\int_0^\infty u dG(u)}$$

where

$$\mu_j = \sum_{\substack{i=1 \\ i \neq j}}^3 p_{ji} \int_0^\infty u dF_{ji}(u), \quad j=1,2,3, \quad \text{and}$$

$$\underline{\pi} = (\pi_1, \pi_2, \pi_3), \quad \sum_{i=1}^3 \pi_i = 1, \quad \pi_i > 0, \quad i=1,2,3, \quad \text{with the relation}$$

$$\underline{\pi} = \underline{\pi} P, \quad \text{in this case}$$

$$(\pi_1, \pi_2, \pi_3) = (\pi_1, \pi_2, \pi_3) \begin{pmatrix} 0 & a & b \\ c & 0 & d \\ p & q & 0 \end{pmatrix}.$$

It may be shown by a general theorem to follow in a later section, that for $\alpha = 0$,

$$P_1 = \frac{\pi_1 \mu_1}{\pi_1 \mu_1 + \pi_2 \mu_2 + \pi_3 \mu_3}.$$

To complete the discussion of the 3-state semi-Markov model, we give the backward, forward, and total time distributions of state 2. There are computed using the previously derived formulas for the distributions in the sequence of states model and the law of conditional probability. We sum up the backward, forward, and total time distributions respectively, each corresponding to a possible path ending in state 2, with each weighted by the asymptotic probability or frequency of that path, given that the cell ends up in state 2. Analogous expressions hold for state 1.

1.7d Forward, backward, and total times.

Let P_2 = asymptotic fraction of cells in state 2.

Define, for $n=0,1,2,\dots$

$$a_n(y) = pa(ca)^n [F_{12} * (F_{12} * F_{21})^{(n)}(y) - F_{12} * (F_{12} * F_{21})^{(n)} * (cF_{21} + dF_{23})(y)]$$

so that

$$a_n(y) = P \left[\begin{array}{c|c} \text{cell of age } y \text{ is in} & \text{cell born in} \\ \hline \text{state 2 for } n^{\text{th}} \text{ time} & \text{state 1} \end{array} \right]$$

and

$$a_n = \frac{\int_0^\infty a_n(y) e^{-\alpha y} dy}{\int_0^\infty [1-G(y)] e^{-\alpha y} dy}.$$

$$a_n = P \left[\begin{array}{c|c} \text{cell is in} & \text{cell born} \\ \hline \text{state 2 for } n^{\text{th}} \text{ time} & \text{in state 1} \end{array} \right]$$

Define, for $n=0,1,2,\dots$

$$b_n(y) = q(ac)^n [(F_{12} * F_{21})^{(n)}(y) - (F_{12} * F_{21})^{(n)} * (cF_{21} + dF_{23})(y)]$$

so that

$$b_n(y) = P \left[\begin{array}{c|c} \text{cell of age } y \text{ is in} & \text{cell born in} \\ \hline \text{state 2 for } n^{\text{th}} \text{ time} & \text{state 2} \end{array} \right]$$

and

$$b_n = \frac{\int_0^\infty b_n(y) e^{-\alpha y} dy}{\int_0^\infty [1-G(y)] e^{-\alpha y} dy}$$

$$b_n = P \left[\begin{array}{c|c} \text{cell is in} & \text{cell born} \\ \hline \text{state 2 for } n^{\text{th}} \text{ time} & \text{in state 2} \end{array} \right] .$$

Then

$$P_2 = \sum_{n=0}^{\infty} (a_n + b_n) \cdot$$

We then have

$$A_2(x) = \frac{1}{P_2} \sum_{n=0}^{\infty} a_n \left[\frac{\int_0^x e^{-\alpha t} [F_{12} * (F_{12} * F_{21})^{(n)}(t) - F_{12} * (F_{12} * F_{21})^{(n)} * (cF_{21} + dF_{23})(t)] dt + \int_x^{\infty} e^{-\alpha t} \left[\int_{t-x}^t d[F_{12} * (F_{21} * F_{12})^{(n)}](x_1) \int_{t-x_1}^{\infty} d[cF_{21} + dF_{23}](x_2) dt \right]}{\int_0^{\infty} e^{-\alpha t} [F_{12} * (F_{21} * F_{12})^{(n)}(t) - F_{12} * (F_{12} * F_{21})^{(n)} * (cF_{21} + dF_{32})(t)] dt} \right]$$

$$\begin{aligned}
& + \frac{b_0}{P_2} \frac{\int_0^\infty e^{-\alpha t} [(cF_{21} + dF_{23})(t+x) - (cF_{21} + dF_{23})(t)] dt}{\int_0^\infty e^{-\alpha t} [U(t) - (cF_{21} + dF_{23})(t)] dt} \\
& + \frac{1}{P_2} \sum_{n=1}^\infty b_n \left[\frac{\int_0^\infty e^{-\alpha t} \left[\int_0^t d[(F_{12} * F_{21})^{(n)}](x_1) \int_{t-x_1}^{t+x-x_1} d[cF_{21} + dF_{23}](x_2) dt \right]}{\int_0^\infty e^{-\alpha t} [(F_{12} * F_{21})^{(n)}(t) - (F_{12} * F_{21})^{(n)} * (cF_{21} + dF_{23})(t)] dt} \right]
\end{aligned}$$

where

$$U(t) = \begin{cases} 1, & t \geq 0 \\ 0, & t < 0 \end{cases}$$

$$\begin{aligned}
c_2(x) &= \frac{1}{P_2} \sum_{n=0}^\infty a_n \left[\frac{\int_0^x e^{-\alpha t} \left[\int_0^t d[(F_{21} * F_{12})^{(n)} * F_{12}](x_1) \int_{t-x_1}^{x-x_1} d[cF_{21} + dF_{23}](x_2) dt \right]}{\int_0^\infty e^{-\alpha t} [F_{12} * (F_{12} * F_{21})^{(n)}(t) - F_{12} * (F_{12} * F_{21})^{(n)} * (cF_{21} + dF_{23})(t)] dt} \right] \\
& + \frac{b_0}{P_2} \frac{\int_0^x e^{-\alpha t} [(cF_{21} + dF_{23})(x) - (cF_{21} + dF_{23})(t)] dt}{\int_0^\infty e^{-\alpha t} [U(t) - (cF_{21} + dF_{23})(t)] dt} \\
& + \frac{1}{P_2} \sum_{n=1}^\infty b_n \left[\frac{\int_0^x e^{-\alpha t} \left[\int_0^t d[(F_{12} * F_{21})^{(n)}](x_1) \int_{t-x_1}^{x-x_1} d[cF_{21} + dF_{23}](x_2) dt \right]}{\int_0^\infty e^{-\alpha t} [(F_{12} * F_{21})^{(n)}(t) - (F_{21} * F_{12})^{(n)} * (cF_{21} + dF_{23})(t)] dt} \right].
\end{aligned}$$

We return to the discussion of the asymptotic fraction of cells in a state, but this time consider the semi-Markov case for an arbitrary number n of states which are available to the cell in its evolution.

1.8 n-state semi-Markov process: $P_R(\alpha)$ as $\alpha \downarrow 1$.

Theorem. Let P be an $n \times n$ irreducible transition matrix with zero trace. Let

$$P_k(\alpha) = \text{asymptotic fraction of cells in state } k, \quad k=1,2,\dots,n,$$

where

$$\alpha: \int_0^\infty e^{-\alpha u} dG(u) = \frac{1}{m}, \quad G \text{ the equivalent cell life distribution.}$$

$$\mu_k = \sum_{\substack{j=1 \\ j \neq k}}^n p_{kj} \int_0^\infty u dF_{kj}(u), \quad k=1,2,\dots,n, \quad \text{where } P = (p_{kj})$$

$$\langle \pi_k \rangle_{k=1}^n \text{ satisfy } \pi_k > 0, \quad k=1,2,\dots,n, \quad \sum_{k=1}^n \pi_k = 1, \quad \text{and for}$$

$$\underline{\pi} = (\pi_1, \pi_2, \dots, \pi_n), \quad \underline{\pi} = \underline{\pi} P.$$

Then, as $\alpha \downarrow 0$,

$$P_k(\alpha) \rightarrow \frac{\pi_k \mu_k}{\sum_{s=1}^n \pi_s \mu_s}, \quad k=1,2,\dots,n.$$

Proof.

$$P_k = \frac{\int_0^\infty q_k(y) e^{-\alpha y} dy}{\int_0^\infty [1-G(y)] e^{-\alpha y} dy} \quad \text{where}$$

$$q_k(y) = P[\text{cell at age } y \text{ is in state } k].$$

Letting $\alpha \downarrow 0$

$$P_K \rightarrow \frac{\int_0^\infty q_k(y) dy}{\int_0^\infty [1-G(y)] dy} .$$

For G_1, G_2 continuous distribution functions on $[0, \infty)$ with $G_1(0) = G_2(0) = 0$, it is immediate that

$$\int_0^\infty [G_1(y) - G_1 * G_2(y)] dy = \int_0^\infty u dG_2(u) .$$

Hence

$$\int_0^\infty q_k(y) dy = \sum_{r=1}^\infty {}_n P_{nk}^{(r)} \mu_k = \frac{\pi_k \mu_k}{\pi_n}$$

where

$${}_n P_{nk}^{(r)} = P \left[\begin{array}{l} \text{a cell considered as a Markov chain hits} \\ \text{state } k \text{ at } r^{\text{th}} \text{ step without hitting} \\ \text{mitotic (nth) state} \end{array} \middle| \begin{array}{l} \text{cell born} \\ \text{at} \\ \text{0th step} \end{array} \right] .$$

See Chung [2], pp. 43-44, 49.

Hence

$$\int_0^\infty [1-G(y)] dy = \frac{1}{\pi_n} \sum_{k=1}^n \pi_k \mu_k$$

and

$$P_k = \frac{\pi_k \mu_k}{\sum_{\ell=1}^n \pi_\ell \mu_\ell} .$$

The theorem is proved.

Two observations are in order. The quantity $\frac{\pi_k}{\pi_n} \mu_k$ is interpreted as the expected visiting time to state k before mitosis, the n th state [2].

We write P_k , for $\alpha = 0$, as

$$P_K = \frac{\mu_k}{\mu_k + \sum_{j \neq k}^n \frac{\pi_j \mu_k}{\pi_k}} .$$

The quantity $\sum_{j \neq k}^n \frac{\pi_j \mu_j}{\pi_k}$ is then the expected time spent in states other than k before returning to k .

The theorem holds for a countable infinity of states, if $\sum_{k=0}^{\infty} \pi_k \mu_k < \infty$, where state 0 is the mitotic state. This form for P_k yields Smith's theorem 5 [7] for our model.

1.9 Convergence in quadratic mean and pairwise correlation.

To conclude Part I, we investigate the asymptotic behavior of the random variables

$$W_R(t) \equiv \frac{Z_R(t)}{E[Z_R(t)]} \quad R=1,2,\dots,n$$

for the general semi-Markov model, which includes the sequence of states model as a special case.

Theorem. Let $m > 1$, and $h''(1) < \infty$. In the semi-Markov model,

$$W_R(t) \rightarrow W_R, \quad R=1,2,\dots,n,$$

a non-degenerate random variable, in quadratic mean.

The pairwise correlations satisfy

$$\lim_{t \rightarrow \infty} \rho(W_R(t), W_S(t)) = \rho(W_R, W_S) = 1, \quad R, S=1,2,\dots,n .$$

Furthermore, $W_S = W_R$ a.e.

Sketch of Proof. See Part II for a similar proof carried out in complete detail. Major steps are given here.

$$\text{Let} \quad G_R(s, t) = \sum_{j=0}^{\infty} P[Z_R(t)=j] s^j$$

$$\text{Let} \quad P_R(t) = P[\text{cell in state R at } t]$$

Let $G(t)$ = equivalent life distribution of the cell.

Then

$$G_R(s, t) = s P_R(t) + 1 - G(t) - P_R(t) + \int_0^t h(G_R(s, t-u)) dG(u)$$

By previous methods, as $t \rightarrow \infty$, since

$$E[Z_R(t)] = \left. \frac{\partial G_R(s, t)}{\partial s} \right|_{s=1},$$

$$E[Z_R(t)] \sim n_R e^{\alpha t}$$

where α satisfies

$$\int_0^{\infty} e^{-\alpha u} dG(u) = \frac{1}{m}$$

and

$$n_R = \frac{\int_0^{\infty} P_R(u) e^{-\alpha u} du}{m \int_0^{\infty} u e^{-\alpha u} dG(u)}.$$

Further

$$E[Z_R^2(t)] = \frac{\partial^2 G_R(s, t)}{\partial s^2} \Big|_{s=1},$$

and we obtain, as shown in Part II,

$$E[Z_R^2(t)] \sim n_R^2 A e^{2\alpha t}$$

where

$$A = \frac{h''(1) \int_0^\infty e^{-2\alpha u} dG(u)}{1-m \int_0^\infty e^{-2\alpha u} dG(u)}.$$

Define

$$G_R(s_1, s_2, t) = \sum_{j,k=0}^{\infty} P[Z_1(t)=j; Z_R(t)=k] s_1^j s_2^k.$$

Then

$$\begin{aligned} G_R(s_1, s_2, t) &= s_1 P_1(t) + s_2 P_R(t) + 1 - G(t) - P_1(t) - P_R(t) \\ &+ \int_0^t h(G_R(s_1, s_2, t-u)) dG(u). \end{aligned}$$

Since

$$E[Z_1(t)Z_R(t)] = \frac{\partial^2 G_R(s_1, s_2, t)}{\partial s_1 \partial s_2} \Big|_{s_1=s_2=1}$$

we obtain

$$E[Z_1(t)Z_R(t)] \sim n_1 n_R A e^{2\alpha t}.$$

This suffices to show that

$$\lim_{t \rightarrow \infty} \rho(W_1(t), W_R(t)) = 1$$

Define

$$G_R(s_1, s_2, t, \tau) = \sum_{j, k=0}^{\infty} P[Z_R(t)=j; Z_R(t+\tau)=k] s_1^j s_2^k .$$

Then

$$\begin{aligned} G_R(s_1, s_2, t, \tau) &= s_1 s_2 P_R(t+\tau) + 1 - G(t+\tau) - P_R(t+\tau) \\ &\quad + \int_0^t h(G_R(s_1, s_2, t-u, \tau)) dG(u) \\ &\quad + s_1 \int_t^{t+\tau} h(G_R(1, s_2, t+\tau-u, 0)) dG(u) . \end{aligned}$$

Since

$$E[Z_R(t)Z_R(t+\tau)] = \frac{\partial^2 G_R(s_1, s_2, t, \tau)}{\partial s_1 \partial s_2} \Big|_{s_1=s_2=1}$$

we obtain

$$E[Z_R(t)Z_R(t+\tau)] \sim n_R^2 A e^{2\alpha t + \alpha \tau}$$

which suffices to show that

$$\lim_{t \rightarrow \infty} E[W_R(t) - W_R(t+\tau)]^2 = 0$$

and hence $W_R(t) \rightarrow W_R$, a random variable, in quadratic mean. Also

$\text{Var}[W_R] = A-1 > 0$, by [3], Ch. 6, sect. 19, so that W_R is non-

degenerate.

That

$$\lim_{t \rightarrow \infty} \rho(W_1(t), W_R(t)) = \rho(W_1, W_R) = 1$$

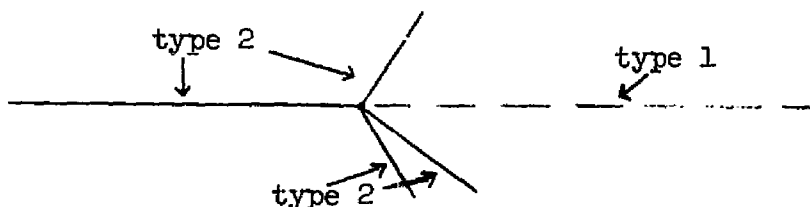
may be obtained by the methods of Part II. Since $E[W_R] = 1$, $E[W_R^2] = A$,

$W_R = W_1$ a.e., $R=1, 2, \dots, n$.

PART II - TOTAL NUMBER OF BIRTHS, $N(t)$

The basic model may be any of those previously considered, since we will now work only with the lifetime distribution function of the entire cell, denoted as before by $G(t) = P[\text{cell lives for age } \leq t]$. We wish to study the total number of cells born by t , denoted by $N(t)$. See Kendall [4], [5] for early results in special cases.

To facilitate computations, we introduce the following variation on the basic model, as indicated by the figure.



A proliferating cell of the type considered in previous models, denoted "type 2", with life distribution $G(t)$, divides into other "type 2" cells, whose number is determined by the generating function $h(s)$, $h'(1) \equiv m > 1$. However, instead of considering that the original cell disappears on division as before, we suppose it is replaced by one "type 1" cell of infinite lifetime. Throughout we assume that at $t = 0$ we initiate the cell growth process with one "type 2" cell. All generating functions set up are conditioned on this fact.

2.1 $m(t), \text{Var}[N(t)]$

Let $Z_1(t)$ = number of type 1 cells at t
 $Z_2(t)$ = number of type 2 cells at t .

Then $Z_1(t) + Z_2(t) = N(t)$ = total number of type 2 cell births by t .

$$m_1(t) = E[Z_1(t)] , m_2(t) = E[Z_2(t)] , m(t) = E[N(t)] .$$

Define

$$G(s_1, s_2, t) = \sum_{j,k=0}^{\infty} P[Z_1(t)=j; Z_2(t)=k] s_1^j s_2^k .$$

Then

$$G(s_1, s_2, t) = s_2(1-G(t)) + s_1 \int_0^t h(G(s_1, s_2, t-u)) dG(u) .$$

Since

$$\left. \frac{\partial G(s_1, s_2, t)}{\partial s_1} \right|_{s_1=s_2=1} = m_1(t) \quad \text{and} \quad \left. \frac{\partial G(s_1, s_2, t)}{\partial s_2} \right|_{s_1=s_2=1} = m_2(t),$$

$$m_1(t) = G(t) + m \int_0^t m_1(t-u) dG(u)$$

$$m_2(t) = 1-G(t) + m \int_0^t m_2(t-u) dG(u)$$

adding,

$$m(t) = 1 + m \int_0^t m(t-u) dG(u) .$$

Assuming $h'(1) \equiv m > 1$, by lemma 1 of the appendix, for t large

$$m_1(t) \sim \left[\frac{\int_0^{\infty} G(u) e^{-\alpha u} du}{m \int_0^{\infty} u e^{-\alpha u} dG(u)} \right] e^{\alpha t} = \frac{e^{\alpha t}}{m^2 \alpha \int_0^{\infty} u e^{-\alpha u} dG(u)} = n_1 e^{\alpha t}$$

$$m_2(t) \sim \left[\frac{\int_0^\infty [1-G(u)] e^{-\alpha u} du}{m \int_0^\infty u e^{-\alpha u} dG(u)} \right] e^{\alpha t} = \frac{(m-1) e^{\alpha t}}{m^2 \alpha \int_0^\infty u e^{-\alpha u} dG(u)} = n_2 e^{\alpha t}$$

$$m(t) \sim \left[\frac{\int_0^\infty e^{-\alpha u} du}{m \int_0^\infty u e^{-\alpha u} dG(u)} \right] e^{\alpha t} = \frac{e^{\alpha t}}{m \alpha \int_0^\infty u e^{-\alpha u} dG(u)} = n_0 e^{\alpha t}$$

and

$$n_1 + n_2 = n_0 .$$

For $h''(1) < \infty$, we know ([3], Ch. 6, sect. 19, 21) that

$$W_2(t) \equiv \frac{Z_2(t)}{n_2 e^{\alpha t}} \rightarrow W_2$$

a random variable, in quadratic mean. In addition, if

$$\int_0^\infty E[W_2(t) - W_2]^2 dt < \infty ,$$

then $W_2(t) \rightarrow W_2$ almost surely. We prove a corresponding result for $N(t)$.

2.2 Convergence of $W_3(t)$.

Theorem. If $h'(1) = m > 1$, $h''(1) < \infty$

$$W_0(t) = \frac{N(t)}{n_0 e^{\alpha t}} \rightarrow W_0 ,$$

a random variable, in quadratic mean.

Proof. Define

$$F(s_1, s_2, t, \tau) = \sum_{0 < j \leq k}^{\infty} P[N(t)=j; N(t+\tau)=k] s_1^j s_2^k .$$

Then

$$F(s_1, s_2, t, \tau) = s_1 s_2 \left[\int_0^t h(F(s_1, s_2, t-u, \tau)) dG(u) + \int_t^{t+\tau} h(K(s_2, t+\tau-u)) dG(u) + 1 - G(t+\tau) \right]$$

where

$$K(s, t) = \sum_{j=1}^{\infty} P[N(t)=j] s^j .$$

We wish to find

$$M_2(t, \tau) \equiv E[N(t)N(t+\tau)] = \frac{\partial^2 F(s_1, s_2, t, \tau)}{\partial s_1 \partial s_2} \Big|_{s_1=s_2=1} .$$

Performing the indicated differentiations,

$$\begin{aligned} M_2(t, \tau) &= 1 + m \int_0^{t+\tau} m(t+\tau-u) dG(u) + m \int_0^t m(t-u) dG(u) \\ &+ h''(1) \int_0^t m(t+\tau-u) m(t-u) dG(u) + m \int_0^t M_2(t-u, \tau) dG(u) . \end{aligned}$$

Using the method of proof of theorem 18.1 of [3], Ch. 6, for t large,

$$M_2(t, \tau) \sim \left[\frac{n_0^2 h''(1) \int_0^{\infty} e^{-2\alpha u} dG(u)}{1 - m \int_0^{\infty} e^{-2\alpha u} dG(u)} \right] e^{2\alpha t + \alpha \tau} .$$

Now we can compute

$$\lim_{t \rightarrow \infty} E[W_0(t+\tau) - W_0(t)]^2 = \lim_{t \rightarrow \infty} \frac{1}{n_0^2} E \left[\frac{N^2(t+\tau)}{e^{2\alpha(t+\tau)}} - \frac{2N(t)N(t+\tau)}{e^{\alpha(t+\tau)+\alpha t}} + \frac{N^2(t)}{e^{2\alpha t}} \right] \rightarrow$$

$$\frac{h''(1) \int_0^\infty e^{-2\alpha u} dG(u)}{1-m \int_0^\infty e^{-2\alpha u} dG(u)} \left[1 + 1 - 2 \frac{e^{2\alpha t + \alpha \tau}}{e^{2\alpha t + \alpha \tau}} \right] = 0, \quad \text{as}$$

$$\int_0^\infty e^{-2\alpha u} dG(u) < \int_0^\infty e^{-\alpha u} dG(u) = \frac{1}{m}.$$

Hence, L_2 completeness shows that

$$W_0(t) = \frac{N(t)}{n_0 e^{\alpha t}} \rightarrow W_0$$

in quadratic mean. The theorem is proved.

The first two moments of W_0 are obtained.

$$E[W_0] = \lim_{t \rightarrow \infty} E \left[\frac{N(t)}{n_0 e^{\alpha t}} \right] = 1$$

$$E[W_0^2] = \lim_{t \rightarrow \infty} E \left[\frac{N^2(t)}{n_0^2 e^{2\alpha t}} \right] = \frac{h''(1) \int_0^\infty e^{-2\alpha u} dG(u)}{1-m \int_0^\infty e^{-2\alpha u} dG(u)}$$

$$\text{Var}[W_0] = \frac{[h''(1)+m] \int_0^\infty e^{-2\alpha u} dG(u) - 1}{1-m \int_0^\infty e^{-2\alpha u} dG(u)} > 0 \text{ by theorem 19.1 of [3],}$$

Ch. 6.

For completeness we state theorem 21.1 of [3], Ch. 6, and its corollary, which hold here.

Theorem. For $m > 1$, $h''(1) < \infty$, G not a lattice distribution, and

$$\int_0^{\infty} E[W_0(t) - W_0]^2 dt < \infty ,$$

then $W_0(t) \rightarrow W_0$ almost surely.

Corollary. For $m > 1$, $h''(1) < \infty$, $G'(t) = g(t)$ and such that

$$\int_0^{\infty} (g(t))^p dt < \infty \text{ for some } p > 1 ,$$

then $W_0(t) \rightarrow W_0$ almost surely.

2.3 Correlation between W_0 and W_2 .

We now wish to find the correlation between the random variables W_0 and W_2 .

Recall that

$$G(s_1, s_2, t) = \sum_{j,k=0}^{\infty} P[Z_1(t)=j; Z_2(t)=k] s_1^j s_2^k$$

satisfies

$$G(s_1, s_2, t) = s_2(1-G(t)) + s_1 \int_0^t h(G(s_1, s_2, t-u)) dG(u) .$$

Since

$$M_{21}(t) = M_{12}(t) \equiv E[Z_1(t)Z_2(t)] = \left. \frac{\partial^2 G(s_1, s_2, t)}{\partial s_1 \partial s_2} \right|_{s_1=s_2=1}$$

$$M_{11}(t) = E[Z_1(t)]^2 = \left. \frac{\partial^2 G(s_1, s_2, t)}{\partial s_1^2} \right|_{s_1=s_2=1}$$

$$M_{22}(t) = E[Z_2(t)]^2 = \left. \frac{\partial^2 G(s_1, s_2, t)}{\partial s_2^2} \right|_{s_1=s_2=1}$$

we obtain the following integral equations.

$$M_{11}(t) = 2m \int_0^t m_1(t-u) dG(u) + h''(1) \int_0^t m_1^2(t-u) dG(u) + m \int_0^t M_{11}(t-u) dG(u)$$

$$M_{22}(t) = h''(1) \int_0^t m_2^2(t-u) dG(u) + m \int_0^t M_{22}(t-u) dG(u)$$

$$M_{12}(t) = m \int_0^t m_2(t-u) dG(u) + h''(1) \int_0^t m_1(t-u) m_2(t-u) dG(u) \\ + m \int_0^t M_{21}(t-u) dG(u) .$$

The method of theorem 18.1 of [3], Ch. 6, yields, for t large,

$$M_{11}(t) \sim \left[\frac{h''(1) n_1^2 \int_0^\infty e^{-2\alpha u} dG(u)}{1-m \int_0^\infty e^{-2\alpha u} dG(u)} \right] e^{2\alpha t}$$

$$M_{22}(t) \sim \left[\frac{h''(1) n_2^2 \int_0^\infty e^{-2\alpha u} dG(u)}{1-m \int_0^\infty e^{-2\alpha u} dG(u)} \right] e^{2\alpha t}$$

$$M_{21}(t) \sim \left[\frac{h''(1) n_1 n_2 \int_0^\infty e^{-2\alpha u} dG(u)}{1-m \int_0^\infty e^{-2\alpha u} dG(u)} \right] e^{2\alpha t} .$$

Since $N(t) = Z_1(t) + Z_2(t)$,

$$\rho(t) \equiv \rho(Z_2(t), N(t)) = \frac{E[Z_1(t)+Z_2(t)][Z_2(t)] - E[Z_1(t)+Z_2(t)]E[Z_2(t)]}{\sqrt{(E[N^2(t)] - E^2[N(t)])(E[Z_2^2(t)] - E^2[Z_2(t)])}} .$$

Let

$$K(s, t) = \sum_{j=1}^{\infty} P[N(t)=j] s^j$$

then

$$K(s, t) = s[1-G(t) + \int_0^t h(K(s, t-u))dG(u)] .$$

For

$$M_2(t) \equiv E[N^2(t)] = \left. \frac{\partial^2 K(s, t)}{\partial s^2} \right|_{s=1} , \text{ we obtain}$$

$$\begin{aligned} M_2(t) &= 2m \int_0^t m(t-u)dG(u) + h''(1) \int_0^t m^2(t-u)dG(u) \\ &+ m \int_0^t M_2(t-u)dG(u) . \end{aligned}$$

For t large

$$M_2(t) \sim \left[\frac{n_0^2 h''(1) \int_0^{\infty} e^{-2\alpha u} dG(u)}{1-m \int_0^{\infty} e^{2\alpha u} dG(u)} \right] e^{2\alpha t}$$

so that writing

$$\rho(t) = \frac{M_{12}(t) + M_{22}(t) - m_1(t)m_2(t) - m_2^2(t)}{\sqrt{(M_2(t) - m^2(t))(M_{22}(t) - m_2^2(t))}} .$$

Putting $c = \int_0^{\infty} e^{-2\alpha u} dG(u)$

$$\lim_{t \rightarrow \infty} \rho(t) \rightarrow \frac{\frac{h''(1)n_1 n_2^c + h''(1)n_2^2}{1-mc} - n_1 n_2 - n_2^2}{\sqrt{\left(\frac{n_0^2 h''(1)c}{1-mc} - n_0^2 \right) \left(\frac{n_2^2 h''(1)c}{1-mc} - n_2^2 \right)}} .$$

Since we have assumed all along that G is not a lattice distribution, we may factor out $(\frac{h''(1)c}{1-mc} - 1) > 0$ in the expression for $\rho(t)$. See [3], Ch. 6, sect. 19.

Thus

$$\rho(t) \rightarrow \frac{n_2(n_1+n_2)(\frac{h''(1)c}{1-mc} - 1)}{n_2(n_1+n_2)(\frac{h''(1)c}{1-mc} - 1)^2} = 1 .$$

We wish to conclude that

$$\rho(t) = \frac{\text{Cov}[W_0(t), W_2(t)]}{\sigma[W_0(t)]\sigma[W_2(t)]} \rightarrow \frac{\text{Cov}[W_0, W_2]}{\sigma[W_0]\sigma[W_2]} = 1 .$$

Since

$$E[W_0(t) - W_0]^2 \rightarrow 0 ,$$

$$E[W_2(t) - W_2]^2 \rightarrow 0 ,$$

we know that

$$E[W_0^2(t)] \rightarrow E[W_0^2] ,$$

$$E[W_2^2(t)] \rightarrow E[W_2^2] .$$

Then it suffices to show that

$$|E[W_0(t)W_2(t)] - E[W_0W_2]| \rightarrow 0 .$$

This follows from

$$\begin{aligned} W_0(t)W_2(t) - W_0W_2 &= W_0(t)W_2(t) - W_0W_2(t) + W_0W_2(t) - W_0W_2 \\ &= W_2(t)(W_0(t) - W_0) + W_0(W_2(t) - W_2) . \end{aligned}$$

We have by the Cauchy-Schwarz inequality

$$|E[W_0(t)W_2(t) - W_0W_2]|^2 \leq E[W_2^2(t)]E[W_0(t) - W_0]^2 + E[W_0^2]E[W_2(t) - W_2]^2 \rightarrow 0$$

since

$$E[W_0^2] < \infty \quad \text{and} \quad E[W_2^2(t)] \rightarrow E[W_2^2] < \infty .$$

Hence

$$\rho(W_0, W_2) = 1 .$$

Comparison of the first two previously derived moments of W_0 with the corresponding moments of W_2 given in [3], Ch. 6, sect. 19 shows that they are the same.

Hence

$$W_2 = W_0 \text{ almost surely.}$$

2.4 m(n) in discrete case.

To check some of the results for the means $m_1(t)$ and $m_2(t)$, suppose we consider the corresponding discrete case, in which a cell divides at the end of a unit interval of time.

The expected value matrix $M = \begin{pmatrix} m_{11} & m_{12} \\ m_{21} & m_{22} \end{pmatrix}$, where

$$m_{ij} = E[\text{number of cells of type } j \text{ issuing from a type } i \text{ cell at its mitosis}]$$

for $j, i=1, 2$

$$M = \begin{pmatrix} 1 & 0 \\ 1 & m \end{pmatrix}$$

$$M^n = \begin{pmatrix} 1 & 0 \\ \frac{m^n - 1}{m - 1} & m^n \end{pmatrix} .$$

Let $G(u) = U(u-1)$, where $U(r) = \begin{cases} 1, & r \geq 0 \\ 0, & r < 0 \end{cases}$, and define $\alpha > 0$:

$$\int_0^\infty e^{-\alpha u} dG(u) = e^{-\alpha} = \frac{1}{m}$$

and we obtain

$$m^n = e^{\alpha n}.$$

Substituting $G(u) = U(u-1)$ into expressions for $m_1(t)$, $m_2(t)$ previously derived, and changing t to n , n large,

$$\left. \begin{aligned} m_1(n) &\sim \frac{e^{\alpha n}}{m \ln(m)} \\ m_2(n) &\sim \frac{(m-1)}{m \ln(m)} e^{\alpha n} \end{aligned} \right\} \text{from continuous case}$$

$$\frac{m_2(n)}{m_1(n)} \sim m-1, \text{ which checks with the matrix case, in which}$$

$$m_1(n) \sim \frac{e^{\alpha n}}{m-1}$$

$$m_2(n) \sim e^{\alpha n}.$$

2.5 $m(t)$ for $m=1$, $m < 1$.

Let

$$K(s, t) = \sum_{j=0}^{\infty} P[N(t)=j] s^j$$

$$K(s, t) = s[(1-G(t)) + \int_0^t h(F(s, t-u)) dG(u)]$$

$$m(t) \equiv E[N(t)] = \left. \frac{\partial K(s, t)}{\partial s} \right|_{s=1}$$

For the case $m=1$,

$$m(t) = 1 + \int_0^t m(t-u) dG(u)$$

and the system is mathematically equivalent to a renewal process. For mild restrictions on G , such as $\int_0^\infty t dG(t) < \infty$, $G(0) = 0$,

$$m(t) \sim \frac{t}{\int_0^\infty u dG(u)}, \quad t \text{ large}.$$

See Chapter 7 of Bellman and Cooke [1].

Case $m < 1$.

$$m(t) = 1 + m \int_0^t m(t-u) dG(u).$$

By lemma 2 of the appendix, for $t \rightarrow \infty$

$$m(t) \rightarrow \frac{1}{1-m}.$$

We check these results for cases $m=1$, $m < 1$, by reverting to the discrete case.

2.6 Convergence and moments of $N(t)$, $m < 1$.

We briefly treat the case $m < 1$.

Theorem. Let G be a distribution function,

$$G(0) = 0.$$

For $m < 1$,

$$N(t) \uparrow N_0, \quad \text{a random variable, a.e.}$$

Proof. $N(t) \uparrow$ a.e.

Since $E[N(t)] = m(t)$ satisfies

$$m(t) = 1 + m \int_0^t m(t-u) dG(u)$$

$m(t) \rightarrow \frac{1}{1-m}$ as $t \rightarrow \infty$, by lemma 2 of the appendix.

Hence $N(t)$ is finite a.e. for all t . After that point t for which $Z_2(t) = 0$ a.e.,

$$N(t) = N(t+\tau) < \infty \text{ for all } \tau > 0 \text{ a.e.}$$

Hence $N(t) \uparrow N_0$, a random variable a.e.

$$E[N_0] = \frac{1}{1-m}.$$

To obtain higher moments of N_0 we assume $h^{(n)}(1) < \infty$ for all $n=1,2,\dots$.

Define

$$K(s,t) = \sum_{j=1}^{\infty} P[N(t)=j] s^j.$$

From

$$K(s,t) = s[1-G(t) + \int_0^t h(K(s,t-u)) dG(u)]$$

we obtain for $M_2(t) \equiv E[N^2(t)]$ the equation

$$M_2(t) = 2m(t)-1 + h''(1) \int_0^t m^2(t-u) dG(u) + m \int_0^t M_2(t-u) dG(u)$$

Claim:

$$\int_0^t m^2(t-u) dG(u) \rightarrow \left(\frac{1}{1-m}\right)^2 \text{ as } t \rightarrow \infty$$

Proof of claim: For $0 < \gamma < 1$,

$$\int_0^t m^2(t-u) dG(u) = \int_0^{t^\gamma} m^2(t-u) dG(u) + \int_{t^\gamma}^t m^2(t-u) dG(u) \quad .$$

Since $m(t) \uparrow$ as $t \uparrow$,

$$\int_{t^\gamma}^t m^2(t-u) dG(u) \leq m^2(t) [G(t) - G(t^\gamma)] \rightarrow \left(\frac{1}{1-m}\right)^2 [G(t) - G(t^\gamma)] \rightarrow 0 \quad ,$$

and

$$m^2(t-t^\gamma) G(t^\gamma) \leq \int_0^{t^\gamma} m^2(t-u) dG(u) \leq m^2(t) G(t^\gamma)$$

which suffices to establish the claim.

Hence

$$M_2(t) = A(t) + \int_0^t M_2(t-u) dG(u)$$

where

$$A(t) \rightarrow \frac{1+m}{1-m} + \frac{h''(1)}{(1-m)^2} \quad \text{as } t \rightarrow \infty$$

and

$$M_2(t) \rightarrow \frac{1}{1-m} \left[\frac{1+m}{1-m} + \frac{h''(1)}{(1-m)^2} \right] = E[N_0^2] \quad .$$

Higher moments are similarly obtained recursively, but no general form for the generating function of N_0 has been obtained.

2.7 $m(n)$ for $m=1$, $m < 1$, in discrete case.

For $m=1$

$$M = \begin{pmatrix} 1 & 0 \\ 1 & 1 \end{pmatrix} \quad , \quad M^n = \begin{pmatrix} 1 & 0 \\ n & 1 \end{pmatrix} \quad \text{and}$$

$m(n) = n+1 \sim n$ for n large.

For $m < 1$

$$M = \begin{pmatrix} 1 & 0 \\ 1 & m \end{pmatrix}, \quad M^n = \begin{pmatrix} 1 & 0 \\ \frac{1-m^n}{1-m} & m^n \end{pmatrix}$$

$$m(n) = \frac{1-m^n}{1-m} + m^n \rightarrow \frac{1}{1-m}, \quad \text{as } n \rightarrow \infty,$$

which checks with the continuous case.

2.8 Moments of $N(t)$, case $m=1$.

We consider the asymptotic moments of $N(t)$ for a simple age dependent branching process with $m=1$. Two theorems from Laplace transform theory will be useful. See Widder [10].

Abelian theorem. If for some $\gamma > 0$

$$\lim_{t \rightarrow \infty} \frac{m(t)}{t^\gamma} = \frac{c}{\Gamma(\gamma+1)}$$

and

$$\mu(s) = \int_0^\infty e^{-st} dm(t)$$

then

$$\lim_{s \downarrow 0} s^\gamma \mu(s) = c.$$

Tauberian theorem. If $m(t)^\uparrow$ is such that

$$\mu(s) = \int_0^\infty e^{-st} dm(t) \quad \text{converges for } \Re(s) > 0$$

and if for some $\gamma > 0$

$$\lim_{s \downarrow 0} s^\gamma \mu(s) = c$$

then

$$\lim_{t \rightarrow \infty} \frac{m(t)}{t^\gamma} = \frac{c}{\Gamma(\gamma+1)}$$

Lemma. Let G be a distribution function, $G(0) = 0$

Let $H(t) \uparrow$ satisfy

$$H(t) = f(t) + \int_0^\infty H(t-u) dG(u)$$

where

$$\int_0^\infty u dG(u) \equiv m_G < \infty ,$$

$f(t)$ is bounded on every finite interval, and

$$\lim_{t \rightarrow \infty} \frac{f(t)}{t^n} = a .$$

Then

$$\lim_{t \rightarrow \infty} \frac{H(t)}{t^{n+1}} = \frac{a}{(n+1)m_G} .$$

Proof. By [3], Ch. 6, appendix, the unique solution bounded on every finite interval is

$$H(t) = \int_0^t f(t-u) dM(u)$$

where

$$M(u) = \sum_{n=0}^{\infty} G^{(n)}(u) .$$

Denoting the Laplace transform of a function g by \tilde{g} , we obtain

$$\tilde{H}(s) = \tilde{F}(s) \tilde{M}(s) = \tilde{F}(s) \left[\frac{1}{1-\tilde{G}(s)} \right] .$$

As $s \downarrow 0$, a Taylor expansion to the first moment yields

$$1-\tilde{G}(s) \sim sm_G$$

and by the Abelian theorem, as $s \downarrow 0$,

$$\tilde{F}(s) \sim \frac{a\Gamma(n+1)}{s^n}$$

$$\tilde{H}(s) \sim \frac{a\Gamma(n+1)}{m_G s^{n+1}}$$

and by the Tauberian theorem

$$\lim_{t \rightarrow \infty} \frac{H(t)}{t^{n+1}} \rightarrow \frac{a\Gamma(n+1)}{m_G \Gamma(n+2)} = \frac{a}{(n+1)m_G} .$$

We may now obtain asymptotic moments of $N(t)$ for $m=1$.

Theorem. If $m=1$,

$$h^{(n)}(1) < \infty , \quad n=1,2,\dots$$

$$\int_0^\infty u dG(u) \equiv m_G < \infty ,$$

then

$$E[N^n(t)] \equiv M_n(t) , \quad n=1,2,\dots$$

$$\lim_{t \rightarrow \infty} \frac{M_n(t)}{t^{2n-1}} = \frac{a_n [h''(1)]^{n-1}}{m_G^{2n-1}}$$

where $a_1=1$, $a_2=\frac{1}{3}$, $a_3=\frac{1}{5}$, $a_4=\frac{17}{105}$, $a_5=\frac{31}{189}$, and the $\{a_n\}$ may be obtained recursively.

Proof. Define

$$K(s,t) = \sum_{j=1}^{\infty} P[N(t)=j] s^j$$

$$K(s,t) = s[1-G(t) + \int_0^t h(K(s,t-u)) dG(u)]$$

$$M_1(t) \equiv m(t) = 1 + \int_0^t m(t-u) dG(u) .$$

From Bellman and Cooke [1], pp. 236-239,

$$\lim_{t \rightarrow \infty} \frac{m(t)}{t} = \frac{1}{m_G}$$

$$M_2(t) = 2[m(t)-1] + h''(1) \int_0^t m^2(t-u) dG(u) + \int_0^t M_2(t-u) dG(u)$$

$$\int_0^t m^2(t-u) dG(u) = \int_0^{t^\gamma} m^2(t-u) dG(u) + \int_{t^\gamma}^t m^2(t-u) dG(u) \text{ for } 0 < \gamma < 1.$$

Now $N(t) \uparrow$, hence $N^n(t) \uparrow$ and $M_n(t) \uparrow$, and

$$\int_{t^\gamma}^t m^2(t-u) dG(u) \leq m^2(t-t^\gamma) [G(t)-G(t^\gamma)] = o(t^2)$$

$$m^2(t-t^\gamma) G(t^\gamma) \leq \int_0^{t^\gamma} m^2(t-u) dG(u) \leq m^2(t) G(t^\gamma)$$

so that

$$M_2(t) = A(t) + \int_0^t M_2(t-u) dG(u)$$

where

$$\lim_{t \rightarrow \infty} \frac{A(t)}{t^2} = \frac{h''(1)}{m_G^2}.$$

By the lemma,

$$\lim_{t \rightarrow \infty} \frac{M_2(t)}{t^3} = \frac{h''(1)}{3 m_G^3}.$$

The general result follows recursively in the same way. No general formula for the $\{a_n\}$ has been obtained.

Note that the result for $M_2(t)$ differs markedly from the renewal theory case, where $h(s) = s$, and with the second moment asymptotic to t^2 and the variance asymptotic to t .

2.9 Moments of $N(n)$ in discrete case, for $m=1, m < 1$.

The two theorems to be given in this section are limit theorems concerning the total number of births in discrete time for cases $m=1$ and $m < 1$. These results are similar to those just given for continuous time.

A cell living at time $n, n=1,2,\dots$ will divide at time $n+0$ into K cells with probability $p_K, K=0,1,2,\dots$ and we let

$$h(s) = \sum_{k=0}^{\infty} p_K s^k, \quad h'(1) \equiv m, \quad \text{and suppose } h^{(\ell)}(1) < \infty$$

for $\ell=1,2,\dots$ and $h''(1) > 0$.

Independence as before is assumed. Each new cell will divide in accord with h at time $(n+1) + 0$.

Let $N(n)$ be the total number of births by time n , $n=1,2,\dots$ starting with one cell at time 0 .

Define

$$K(s,n) = \sum_{j=1}^{\infty} P[N(n)=j] s^j, \quad n=1,2,\dots$$

By taking $G(u) = \begin{cases} 1, & u > 1 \\ 0, & u \leq 1 \end{cases}$ in the equation in continuous time t , $t > 1$

$$K(s,t) = s[1-G(t) + \int_0^t h(K(s,t-u))dG(u)]$$

and setting $t=n+1$, we obtain

$$K(s,n+1) = s h(K(s,n)) .$$

We proceed to cases $m=1$ and $m < 1$.

To treat the case $m=1$, we need the following particular case of the lemma of Part II applied to discrete time.

Corollary 1. Let f^\uparrow be a function on the positive integers satisfying, for $K \rightarrow \infty$, $n=1,2,\dots$, and $a > 0$ and

$$f(K+1) = g(K) + f(K)$$

$$\lim_{K \rightarrow \infty} \frac{g(K)}{K^n} = a .$$

Then, as $K \rightarrow \infty$,

$$\lim_{K \rightarrow \infty} \frac{f(K)}{K^{n+1}} = \frac{a}{n+1} .$$

Theorem 1. Let

$$E[N(n)] = M(n)$$

$$E[N^r(n)] = M_r(n), \quad r=2,3,\dots$$

Then if $m=1$, we have

$$M(n) = n$$

and

$$\lim_{n \rightarrow \infty} \frac{M_r(n)}{n^{2r-1}} = a_r [h''(1)]^{r-1},$$

where the $\{a_r\}_{r=2}^{\infty}$ are the a 's in the analogous continuous time theorem for $N(t)$, $m=1$.

Proof sketch. From $K(s, n+1) = sh(K(s, n))$, since

$$\left. \frac{\partial K(s, n)}{\partial s} \right|_{s=1} = M(n),$$

$$M(n+1) = 1 + M(n), \quad m(1) = 1$$

Hence

$$M(n) = n$$

$$M_2(n+1) = 2 M(n) + h''(1) M^2(n) + M_2(n).$$

By the lemma, since $N(n) \uparrow$ implies $N^k(n) \uparrow$ implies $M_k(n) \uparrow$,

$$\lim_{n \rightarrow \infty} \frac{M_2(n)}{n^3} = \frac{h''(1)}{3} \quad k=1,2,\dots$$

Continuing in this recursive manner, the result may be established.

The results for the case $m < 1$ are essentially identical with those for the continuous case.

Theorem 2. If $m < 1$, as $n \rightarrow \infty$,

$$M(n) \rightarrow \frac{1}{1-m}$$

$$M_r(n) \rightarrow b_r \quad r=2,3,\dots$$

where the $\langle b_r \rangle_{r=2}^{\infty}$ are the same as in the continuous case, $m < 1$.

Proof. From $K(s, n+1) = sh(K(s, n))$,

$$M(n+1) = 1 + m M(n) .$$

We may apply lemma 2 of the appendix for $G(u) = \begin{cases} 1, & u > 1 \\ 0, & u < 1 \end{cases}$ to obtain

$$M(n) \rightarrow \frac{1}{1-m} .$$

$$M_2(n+1) = 2mM(n) + h''(1)M^2(n) + mM_2(n)$$

and again applying lemma 2 of the appendix,

$$M_2(n) \rightarrow \frac{1}{1-m} \left[\frac{1+m}{1-m} + \frac{h''(1)}{(1-m)^2} \right]$$

and so on recursively to establish the result.

PART III - TWO TYPES OF CELLS

3.1 Model I.

This section discusses two models for cell growth in an expanding population involving the proliferation of two types of cells. In the first model, a "type 1" cell has a non-lattice life distribution H , $H(0) = 0$ and is incapable of proliferation. At the end of its life period, it is absorbed. A "type 2" cell, with non-lattice distribution G , $G(0) = 0$ is capable of proliferation. At the end of mitosis it gives rise to

2 clusters of "type 1" cells - with probability q^2

1 cluster of "type 1" cells and a cluster of "type 2" cells - with
probability $2pq$

2 clusters of "type 2" cells - with probability p^2

where $p+q = 1$, $p > 0$, $q > 0$, and a cluster of type 2 cells is a collection of those cells, containing k cells with probability p_k , $k=0,1,\dots$. Define

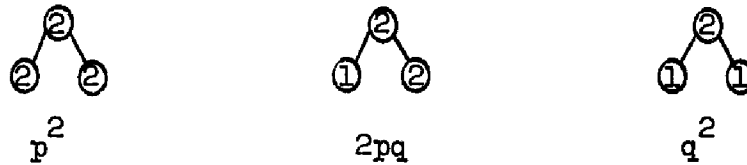
$$h(s) = \sum_{k=0}^{\infty} p_k s^k, \quad \text{and} \quad h'(1) \equiv m, \quad h''(1) < \infty.$$

Similarly, a cluster of type 1 cells contains k type 1 cells with probability q_k , and define

$$b(s) \equiv \sum_{k=0}^{\infty} q_k s^k, \quad b'(1) \equiv d$$

Each type of cell and cluster forms independently of the state of the system. The cells are independent of each other. See Kendall [6].

For $h(s) = b(s) = s$ the process may be represented schematically as follows



Define, given that at $t=0$, the process starts with one newly born type 2 cell,

$Z_1(t)$ = number of "type 1" cells at t

$Z_2(t)$ = number of "type 2" cells at t

$N_2(t)$ = number of "type 2" cells born by t

$N_1(t)$ = number of "type 1" cells born by t

3.2 $E[Z_1(t)], E[Z_2(t)]$.

The first moments of these quantities are obtained for large t , and are related to the corresponding discrete time case results. A discussion of convergence in quadratic mean indicates also the asymptotic second moments.

Before starting the computations, we note that the "type 2" cells form a process which is independent of the type 1 cells as follows.

With probability q^2 - 0 "type 2" cells are emitted on
division of a "type 2" cell

$2pq$ - 1 cluster of "type 2" cells is emitted

p^2 - 2 clusters of "type 2" cells are emitted.

The equivalent generating function for the number of new "type 2" cells created on division of a "type 2" cell is

$$f(r) = g(h(r))$$

where $g(s) = q^2 + 2pqs + p^2s^2$ and $h(r) = \sum_{j=0}^{\infty} p_j r^j$.

Hence, as done in previous sections, the backward, forward, and total time distributions and asymptotic mean and variance of the number of "type 2" cells in a state may be computed, if the type 2 cell progresses through n states, the k^{th} state life characterized by its distribution F_k , $k=1,2,\dots,n$. Here $G = F_1 * \dots * F_n$ if we deal with the sequence of states model, and G is the equivalent life distribution of the cell in the semi-Markov case.

Throughout, all generating functions depending on the time are conditioned on the event that at $t=0$, the process begins with one newly born cell of type 2 or one of type 1, as will be specified.

Define

$$G_1(s_1, s_2, t) = \sum_{j,k=0}^{\infty} P[Z_1(t)=j; Z_2(t)=k | \text{type 1 at } t=0] s_1^j s_2^k$$

$$G_1(s_1, s_2, t) = s_1[1-H(t)] + H(t)$$

$$G_2(s_1, s_2, t) = s_2(1-G(t)) + \int_0^t [q^2 b^2(G_1(s_1, s_2, t-u)) + 2pqb(G_1(s_1, s_2, t-u)) \\ h(G_2(s_1, s_2, t-u)) + p^2 h^2(G_2(s_1, s_2, t-u))] dG(u)$$

Let

$$m_1(t) \equiv E[Z_1(t)] = \left. \frac{\partial G_2(s_1, s_2, t)}{\partial s_1} \right|_{s_1=s_2=1}$$

$$m_2(t) \equiv E[Z_2(t)] = \left. \frac{\partial G_2(s_1, s_2, t)}{\partial s_2} \right|_{s_1=s_2=1}$$

$$m_1(t) = 2qd \int_0^t [1-H(t-u)] dG(u) + 2pm \int_0^t m_1(t-u) dG(u)$$

or

$$m_1(t) = 2qd[G(t) - G * H(t)] + 2pm \int_0^t m_1(t-u) dG(u)$$

$$m_2(t) = 1-G(t) + 2pm \int_0^t m_2(t-u) dG(u) .$$

To treat the case of an expanding cell population, assume that $2pm > 1$, and we define

$$\alpha : \int_0^\infty e^{-\alpha u} dG(u) = \frac{1}{2pm} .$$

Then, for t large, by lemma 1 of the appendix,

$$m_1(t) \sim \left[\frac{2qd \int_0^\infty [G(u) - (G*H)(u)] e^{-\alpha u} du}{2pm \int_0^\infty u e^{-\alpha u} dG(u)} \right] e^{\alpha t} = n_1 e^{\alpha t}$$

$$m_2(t) \sim \left[\frac{\int_0^\infty [1-G(u)] e^{-\alpha u} du}{2pm \int_0^\infty u e^{-\alpha u} dG(u)} \right] e^{\alpha t} = \frac{\frac{1}{\alpha} [1 - \frac{1}{2pm}] e^{\alpha t}}{2pm \int_0^\infty u e^{-\alpha u} dG(u)} = n_2 e^{\alpha t}$$

3.3 Comparison with discrete case.

We compare these results with those in the discrete case.

Let X = number of "type 2" cells emitted from a "type 2" cell on division.

$$E[X] = E[X | \text{"type 1" cluster emitted}] P[\text{"type 1" cluster emitted}] +$$

$$E[X | 0 \text{ "type 1" clusters emitted}]$$

$$P[0 \text{ "type 1" clusters emitted}]$$

$$E[X] = 2pqm + p^2 2m = 2pm.$$

Let Y = number of "type 1" cells emitted when a "type 2" divides.

$$E[Y] = d \cdot 2pq + 2d \cdot q^2 = 2qd .$$

The expectation matrix M is

$$M = \begin{pmatrix} 1 & 0 \\ 2qd & 2pm \end{pmatrix}$$

where we assume for simplicity that $H = 0$, that is, a type 1 cell has infinite life.

$$M^n = \begin{pmatrix} 1 & 0 \\ 2qd \left[\frac{(2pm)^n - 1}{2pm - 1} \right] & (2pm)^n \end{pmatrix} .$$

$$\text{Let } G(t) = U(t-1) , \quad U(s) = \begin{cases} 1, & s \geq 0 \\ 0, & s < 0 \end{cases} .$$

Let t correspond to n , the n^{th} step of a discrete process. Thus the continuous case is changed to the discrete.

$$e^{-\alpha} = \frac{1}{2pm} ,$$

$$m_1(t) \sim m_1(n) \sim \frac{2qd}{\frac{1}{2pm} \alpha} e^{\alpha n} = \frac{qd}{pm\alpha} e^{\alpha n}$$

$$m_2(t) \sim m_2(n) \sim \frac{1}{\alpha} \left[1 - \frac{1}{2pm} \right] e^{\alpha n}$$

$$\frac{m_1(n)}{m_2(n)} \sim \frac{2qd}{2pm-1} .$$

From the matrix M ,

$$m_1(n) \sim \frac{2qd}{2pm-1} (2pm)^n = \frac{2qd}{2pm-1} e^{\alpha n}$$

$$m_2(n) \sim (2pm)^n = e^{\alpha n}$$

$$\frac{m_1(n)}{m_2(n)} \sim \frac{2qd}{2pm-1} . \quad \text{The ratios check.}$$

This leads to

3.4 Comparison with results of Snow.

Lemma. The ratio of the components of the left eigenvector corresponding to the largest eigenvalue of M is that of the asymptotic ratio of the mean numbers of "type 1" and "type 2" cells in the continuous case, in which $H = 0$ [i.e., type 1 cells have infinite life].

That is

$$\begin{aligned} \text{if} \quad & (\alpha, \beta)M = \lambda_{\max}(\alpha, \beta) \\ \text{then} \quad & \frac{\alpha}{\beta} \sim \frac{m_1(t)}{m_2(t)} , \quad t \text{ large} . \end{aligned}$$

Proof.

$$M = \begin{pmatrix} 1 & 0 \\ 2qd & 2pm \end{pmatrix} , \quad \lambda_{\max} = 2pm$$

$$(\alpha, \beta)M = 2pm(\alpha, \beta)$$

$$\alpha + 2qd\beta = 2pm\alpha$$

$$\frac{\alpha}{\beta} = \frac{2qd}{2pm-1} \sim \frac{m_1(t)}{m_2(t)} .$$

Snow [8] presumably has general results of the type in the lemma, but for the "irreducible" case, that is, if M is now normalized to form a transition matrix, it would be irreducible. In the case treated here, the states of M do not communicate. See also [3], Ch. 5.

3.5 $E[N_1(t)], E[N_2(t)]$.

Let

$$B(s, t) = \sum_{j=0}^{\infty} P[N_2(t)=j] s^j$$

$$B(s, t) = s[1-G(t) + \int_0^t f(B(s, t-u)) dG(u)]$$

where

$$f(x) = g(h(x)), \quad g(s) = q^2 + 2pqs + p^2 s^2 \quad \text{and}$$

$h(x) = \sum_{k=0}^{\infty} p_k x^k$. This has been done in an earlier section. For t large, and $\alpha : \int_0^{\infty} e^{-\alpha u} dG(u) = \frac{1}{2pm}$

$$E[N_2(t)] \sim \left[\frac{1}{2pm\alpha \int_0^{\infty} u e^{-\alpha u} dG(u)} \right] e^{\alpha t} = n_{02} e^{\alpha t}.$$

To find $E[N_1(t)]$, set $H = 0$, so that $G_1(s_1, s_2, t) = s_1$, which is equivalent to letting a type 1 cell have infinite life.

$$E[N_1(t)] \sim \left[\frac{\frac{2qd}{2pm\alpha}}{2pm \int_0^{\infty} u e^{-\alpha u} dG(u)} \right] e^{\alpha t} = n_{01} e^{\alpha t}.$$

These results can be checked with the discrete case, and a lemma like the above proved.

3.6 Convergence in quadratic mean and asymptotic correlations.

Given $h''(1) < \infty$, $2pm > 1$, we wish to show that, $t \rightarrow \infty$,

$$W_1(t) = \frac{Z_1(t)}{n_1 e^{\alpha t}} \rightarrow W_1 \quad \text{in quadratic mean}$$

$$W_2(t) = \frac{Z_2(t)}{n_2 e^{\alpha t}} \rightarrow W_2 \quad "$$

$$W_{01}(t) = \frac{N_1(t)}{n_{01} e^{\alpha t}} \rightarrow W_{01} \quad "$$

$$W_{02}(t) = \frac{N_2(t)}{n_{02} e^{\alpha t}} \rightarrow W_{02} \quad "$$

where

$$\alpha : \int_0^\infty e^{-\alpha u} dG(u) = \frac{1}{2pm} .$$

The computation of all new generating functions to follow assumes that at $t = 0$, the process starts with one cell of type 2.

We shall let the notations $G_1(s_1, s_2, t)$ and $G_2(s_1, s_2, t)$ stand for the generating functions which they stood for in the preceeding section on two cell types.

Define

$$B(s_1, s_2, t, \tau) = \sum_{j, k=0}^{\infty} P[Z_1(t)=j; Z_1(t+\tau)=k] s_1^j s_2^k .$$

Then

$$\begin{aligned}
B(s_1, s_2, t, \tau) = & 1 - G(t + \tau) + \int_0^t [q^2 b^2(G_1(s_1, 1, t - u)) + 2pq b(G_1(s_1, 1, t - u)) \\
& h(B(s_1, s_2, t - u, \tau)) + p^2 h^2(B(s_1, s_2, t - u, \tau))] dG(u) \\
& + \int_t^{t+\tau} [q^2 b^2(G_1(s_2, 1, t + \tau - u)) + 2pq b(G_1(s_2, 1, t + \tau - u)) h(G_2(s_2, 1, t + \tau - u)) \\
& + p^2 h^2(G_2(s_2, 1, t + \tau - u))] dG(u) .
\end{aligned}$$

Since

$$\left. \frac{\partial^2 B(s_1, s_2, t, \tau)}{\partial s_1 \partial s_2} \right|_{s_2=s_1=1} = E[Z_1(t)Z_1(t+\tau)] ,$$

we find, using the method in theorem 18.1 of [3], Ch. 6, that, for large t ,

$$E[Z_1(t)Z_1(t+\tau)] \sim \left[\frac{2pn_1^2 \int_0^\infty e^{-2\alpha u} dG(u) [h''(1) + pm^2]}{1 - 2pm \int_0^\infty e^{-2\alpha u} dG(u)} \right] e^{2\alpha t + \alpha \tau} .$$

Let

$$C(s_1, s_2, t, \tau) = \sum_{j,k=0}^{\infty} P[Z_2(t)=j; Z_2(t+\tau)=k] s_1^j s_2^k$$

$$\begin{aligned}
C(s_1, s_2, t, \tau) = & s_1 s_2 [1 - G(t + \tau)] + \int_0^t [q^2 + 2pq h(C(s_1, s_2, t - u, \tau)) \\
& + p^2 h^2(C(s_1, s_2, t - u, \tau))] dG(u) \\
& + s_1 \int_t^{t+\tau} [q^2 + 2pq h(G_2(1, s_2, t + \tau - u)) + p^2 h^2(G_2(1, s_2, t + \tau - u))] dG(u)
\end{aligned}$$

$$\left. \frac{\partial^2 C(s_1, s_2, t, \tau)}{\partial s_1 \partial s_2} \right|_{s_1=s_2=1} = E[Z_2(t)Z_2(t+\tau)]$$

and

$$E[Z_2(t)Z_2(t+\tau)] \sim \left[\frac{2pn_2^2 \int_0^\infty e^{-2\alpha u} dG(u) [h''(1) + pm^2]}{1 - 2pm \int_0^\infty e^{-2\alpha u} dG(u)} \right] e^{2\alpha t + \alpha \tau}.$$

Let

$$\begin{aligned} D(s_1, s_2, t, \tau) &= \sum_{k \geq j \geq 0}^\infty P[N_1(t)=j; N_1(t+\tau)=k] s_1^j s_2^k \\ D(s_1, s_2, t, \tau) &= 1 - G(t+\tau) + \int_0^t [q^2 b^2(s_1 s_2) + 2pqb(s_1 s_2)h(D(s_1, s_2, t-u, \tau)) \\ &\quad + p^2 h^2(D(s_1, s_2, t-u, \tau))] dG(u) \\ &\quad + \int_t^{t+\tau} [q^2 b^2(s_2) + 2pqb(s_2)h(R(s_2, t+\tau-u)) \\ &\quad + p^2 h^2(R(s_2, t+\tau-u))] dG(u) \end{aligned}$$

where

$$R(s, t) = D(s, 1, t, 0)$$

$$\begin{aligned} \frac{\partial^2 D(s_1, s_2, t, \tau)}{\partial s_1 \partial s_2} \Big|_{s_1=s_2=1} &= E[N_1(t)N_1(t+\tau)] \\ E[N_1(t)N_1(t+\tau)] &\sim \left[\frac{2pn_{01}^2 \int_0^\infty e^{-2\alpha u} dG(u) [h''(1) + pm^2]}{1 - 2pm \int_0^\infty e^{-2\alpha u} dG(u)} \right] e^{2\alpha t + \alpha \tau}. \end{aligned}$$

Let

$$H(s_1, s_2, t, \tau) = \sum_{k \geq j \geq 1}^{\infty} P[N_2(t)=j; N_2(t+\tau)=k] s_1^j s_2^k$$

$$\begin{aligned} H(s_1, s_2, t, \tau) = & s_1 s_2 [1 - G(t+\tau) + \int_0^t [q^2 + 2pqh(H(s_1, s_2, t-u, \tau)) \\ & + p^2 h^2(H(s_1, s_2, t-u, \tau))] dG(u) \\ & + \int_t^{t+\tau} [q^2 + 2pqh(K(s_2, t+\tau-u)) + p^2 h^2(K(s_2, t+\tau-u))] dG(u) \end{aligned}$$

where we may take

$$K(s, t) = H(s, 1, t, 0)$$

$$\begin{aligned} \frac{\partial H(s_1, s_2, t, \tau)}{\partial s_1 \partial s_2} \Big|_{s_1=s_2=1} &= E[N_2(t)N_2(t+\tau)] \\ E[N_2(t)N_2(t+\tau)] &\sim \left[\frac{2pn_{02}^2 \int_0^\infty e^{-2\alpha u} dG(u) [h''(1) + pm^2]}{1 - 2pm \int_0^\infty e^{-2\alpha u} dG(u)} \right] e^{2\alpha t + \alpha \tau} . \end{aligned}$$

Applying the above formulas, we see that

$$E[W_1(t) - W_1(t+\tau)]^2 \rightarrow 0$$

$$E[W_2(t) - W_2(t+\tau)]^2 \rightarrow 0$$

$$E[W_{01}(t) - W_{01}(t+\tau)]^2 \rightarrow 0$$

$$E[W_{02}(t) - W_{02}(t+\tau)]^2 \rightarrow 0$$

so that $W_1(t) \rightarrow W_1$, $W_2(t) \rightarrow W_2$, $W_{01}(t) \rightarrow W_{01}$, $W_{02}(t) \rightarrow W_{02}$ in quadratic mean.

Pairwise correlation among W_1, W_2, W_{01}, W_{02} .

We explicitly indicate how to find the correlation only between W_1 and W_2 . The other five follow similarly.

Let

$$M_{11}(t) \equiv E[Z_1^2(t)] = \frac{\partial^2 G_2(s_1, s_2, t)}{\partial s_1^2} \Big|_{s_1=s_2=1}$$

$$M_{22}(t) \equiv E[Z_2^2(t)] = \frac{\partial^2 G_2(s_1, s_2, t)}{\partial s_2^2} \Big|_{s_1=s_2=1}$$

$$M_{12}(t) = M_{21}(t) \equiv E[Z_1(t)Z_2(t)] = \frac{\partial^2 G_2(s_1, s_2, t)}{\partial s_1 \partial s_2} \Big|_{s_1=s_2=1}$$

Let

$$\int_0^\infty e^{-2\alpha u} dG(u) = c$$

$$M_{11}(t) \sim \left[\frac{2pn_1^2 c [h''(1) + pm^2]}{1-2pmc} \right] e^{2\alpha t}$$

$$M_{22}(t) \sim \left[\frac{2pn_2^2 c [h''(1) + pm^2]}{1-2pmc} \right] e^{2\alpha t}$$

$$M_{12}(t) \sim \left[\frac{2pn_1 n_2 c [h''(1) + pm^2]}{1-2pmc} \right] e^{2\alpha t}$$

$$\rho(Z_1(t), Z_2(t)) = \frac{M_{12}(t) - m_1(t)m_2(t)}{\sqrt{(M_{11}(t) - m_1^2(t))(M_{22}(t) - m_2^2(t))}}$$

$$\rho(Z_1(t), Z_2(t)) \rightarrow \frac{n_1 n_2 \left[\frac{2pc(h''(1) + pm^2)}{1-2pmc} - 1 \right]}{n_1 n_2 \left[\frac{2pc(h''(1) + pm^2)}{1-2pmc} - 1 \right]} = 1,$$

since we have the following lemma.

Lemma.

$$\frac{2pc(h''(1)+pm^2)}{1-2pmc} - 1 > 0 .$$

Proof. First note, by the Cauchy-Schwarz inequality

$$c = \int_0^\infty e^{-2\alpha u} dG(u) > \left[\int_0^\infty e^{-\alpha u} dG(u) \right]^2 = \frac{1}{4p^2 m^2}$$

$$\frac{2pc(h''(1)+pm^2)}{1-2pmc} - 1 = \frac{c[2ph''(1)+2p^2 m^2 + 2pm] - 1}{1-2pmc} .$$

It suffices to show

$$c[2ph''(1)+2p^2 m^2 + 2pm] > 1$$

or to show

$$\frac{2ph''(1) + 2p^2 m^2 + 2pm}{4p^2 m^2} > 1$$

or

$$\frac{h''(1) + pm^2 + m}{2pm^2} > 1$$

or

$$h''(1) + m > pm^2$$

but

$$h''(1) + m > m^2 > pm^2 , \quad \text{as}$$

$h''(1)$ is the second factorial moment of h .

In order to show that

$$\rho(W_1(t), W_2(t)) = \frac{\text{Cov}[W_1(t), W_2(t)]}{\sigma[W_1(t)]\sigma[W_2(t)]} \rightarrow \frac{\text{Cov}[W_1, W_2]}{\sigma[W_1]\sigma[W_2]} = 1$$

we use the same reasoning as in the section on total number of births with one cell type.

$$\begin{aligned} \text{Since} \quad & E[W_1(t) - W_1]^2 \rightarrow 0 \\ & E[W_2(t) - W_2]^2 \rightarrow 0 \end{aligned}$$

we have

$$\begin{aligned} E[W_1^2(t)] &\rightarrow E[W_1^2] \\ E[W_2^2(t)] &\rightarrow E[W_2^2] . \end{aligned}$$

It suffices to show that

$$|E[W_1(t)W_2(t) - W_1W_2]| \rightarrow 0 .$$

Write

$$W_1(t)W_2(t) - W_1W_2 = W_2(t)[W_1(t) - W_1] + W_1[W_2(t) - W_2] .$$

By the Cauchy-Schwarz inequality,

$$|E[W_1(t)W_2(t) - W_1W_2]|^2 \leq E[W_2^2(t)]E[W_1(t) - W_1]^2 + E[W_1^2]E[W_2(t) - W_2]^2 \rightarrow 0$$

since

$$E[W_1^2] < \infty \quad \text{and} \quad E[W_2^2(t)] \rightarrow E[W_2^2] < \infty .$$

Hence

$$\rho(W_1, W_2) = 1 .$$

All the other five correlations are 1.

Since

$$E[W_1] = E[W_2] = E[W_{01}] = E[W_{02}] = 1$$

and, by the previous section,

$$\text{Var}[W_1] = \text{Var}[W_2] = \text{Var}[W_{01}] = \text{Var}[W_{02}] =$$

$$\frac{2p \int_0^\infty e^{-2\alpha u} dG(u) [h''(1) + pm^2 + m] - 1}{1 - 2pm \int_0^\infty e^{-2\alpha u} dG(u)} > 0$$

$$W_1 = W_2 = W_{01} = W_{02} \quad \text{a.s.}$$

In the discrete case, $m > 1$, convergence of $\lim_{n \rightarrow \infty} \frac{Z_k(n)}{\lambda_{\max}^n} \rightarrow w_k$, a random variable in quadratic mean, is discussed in [3], Ch. 2, for multiple types $k=1,2,\dots,k_0$. Here λ_{\max} is the largest eigenvalue of a relevant expectation matrix.

3.7 Model II.

The second model of two cell types to be considered is similar to the first. Using the same notation as in the previous case, the process may be described as follows. At the end of mitosis of a type 2 cell, the progeny may be

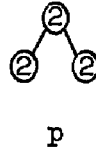
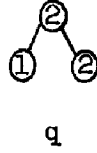
1 cluster of "type 1" cells and 1 cluster of "type 2"

cells - with probability q

2 clusters of "type 2" cells - with probability p

$p+q=1$.

In case $h(s) = s$, $b(s) = s$, we may represent the process schematically as



3.8 $E[Z_1(t)], E[Z_2(t)]$.

Let

$$G_1(s_1, s_2, t) = \sum_{j,k=0} P[Z_1(t)=j; Z_2(t)=k \mid \text{type 1 at } t=0] s_1^j s_2^k .$$

Then

$$G_1(s_1, s_2, t) = s_1[1-H(t)] + H(t)$$

$$G_2(s_1, s_2, t) = s_2[1-G(t)] + \int_0^t [ph^2(G_2(s_1, s_2, t-u)) + qb(G_1(s_1, s_2, t-u))h(G_2(s_1, s_2, t-u))]dG(u) .$$

Assuming an expanding cell population, or $m(p+1) > 1$,

$$m_1(t) \sim \left[\frac{qd \int_0^\infty [G(u)-G \cdot H(u)] e^{-\alpha u} du}{m(p+1) \int_0^\infty u e^{-\alpha u} dG(u)} \right] e^{\alpha t} = n_1 e^{\alpha t}$$

$$m_2(t) \sim \left[\frac{\int_0^\infty [1-G(u)] e^{-\alpha u} du}{m(p+1) \int_0^\infty u e^{-\alpha u} dG(u)} \right] e^{\alpha t} = n_2 e^{\alpha t}$$

where α satisfies $\int_0^\infty e^{-\alpha u} dG(u) = \frac{1}{m(p+1)}$ and so

$$n_2 = \frac{\frac{1}{\alpha} \left[1 - \frac{1}{m(p+1)} \right]}{m(p+1) \int_0^\infty u e^{-\alpha u} dG(u)} .$$

3.9 Comparison with discrete case.

Checking with the discrete case as before, we obtain

$$M = \begin{pmatrix} 1 & 0 \\ qd & m(p+1) \end{pmatrix}$$

$$M^n = \begin{pmatrix} 1 & 0 \\ qd \left[\frac{m(p+1)^n - 1}{m(p+1) - 1} \right] & [m(p+1)]^n \end{pmatrix}$$

and

$$\frac{m_1(n)}{m_2(n)} \sim \frac{qd}{m(p+1) - 1}$$

for both the discrete matrix case and the "discretized" continuous case.

We thus obtain

Lemma. If

$$(\alpha, \beta)M = \lambda_{\max}(\alpha, \beta) = m(p+1)(\alpha, \beta) ,$$

then

$$\frac{qd}{m(p+1) - 1} = \frac{\alpha}{\beta} \sim \frac{m_1(t)}{m_2(t)} , \quad t \rightarrow \infty .$$

3.10 $E[N_1(t)], E[N_2(t)]$.

Let

$$B(s, t) = \sum_{j=0}^{\infty} P[N_2(t)=j] s^j$$

$$B(s, t) = s [1 - G(t) + \int_0^t [ph^2(B(s, t-u)) + qh(B(s, t-u))] dG(u)]$$

$$E[N_2(t)] \sim \left[\frac{1}{m(p+1)\alpha \int_0^{\infty} u e^{-\alpha u} dG(u)} \right] e^{\alpha t} = n_{02} e^{\alpha t}.$$

To find $E[N_1(t)]$, set $H=0$, so that $G_1(s_1, s_2, t) = s_1$. With this change,

$$E[N_1(t)] = \left. \frac{\partial G_2(s_1, s_2, t)}{\partial s_1} \right|_{s_1=s_2=1}$$

and

$$E[N_1(t)] \sim \left[\frac{\frac{qd}{m(p+1)\alpha}}{m(p+1) \int_0^{\infty} u e^{-\alpha u} dG(u)} \right] e^{\alpha t} = n_{01} e^{\alpha t}$$

3.11 Convergence in quadratic mean and asymptotic correlations.

The arguments are as in the previous two cell type model.

Altered steps are sketched. As before, we study $W_i(t), W_{0i}(t), i=1,2$.

Define

$$B(s_1, s_2, t, \tau) = \sum_{j,k=0}^{\infty} P[Z_1(t)=j; Z_1(t+\tau)=k] s_1^j s_2^k$$

$$\begin{aligned}
B(s_1, s_2, t, \tau) &= 1 - G(t + \tau) + \int_0^t [ph^2(B(s_1, s_2, t-u, \tau)) + \\
&+ qb(G_1(s_1, 1, t-u))h(B(s_1, s_2, t-u, \tau))]dG(u) \\
&+ s_1 \int_t^{t+\tau} [ph^2(G_2(s_2, 1, t+\tau-u)) + \\
&+ qb(G_1(s_2, 1, t+\tau-u))h(G_2(s_2, 1, t+\tau-u))]dG(u)
\end{aligned}$$

$$E[Z_1(t)Z_1(t+\tau)] = \frac{\partial^2 B(s_1, s_2, t, \tau)}{\partial s_1 \partial s_2} \Big|_{s_1=s_2=1}$$

$$E[Z_1(t)Z_1(t+\tau)] \sim n_1^2 A e^{2\alpha t + \alpha \tau}$$

where

$$A = \frac{[h''(1)[1+p] + 2pm^2] \int_0^\infty e^{-2\alpha u} dG(u)}{1-m(p+1) \int_0^\infty e^{-2\alpha u} dG(u)}.$$

Define

$$C(s_1, s_2, t, \tau) = \sum_{j,k=0}^{\infty} P[Z_2(t)=j; Z_2(t+\tau)=k] s_1^j s_2^k$$

$$\begin{aligned}
C(s_1, s_2, t, \tau) &= s_1 s_2 [1 - G(t + \tau)] + \int_0^t [ph^2(C(s_1, s_2, t-u, \tau)) \\
&+ qh(C(s_1, s_2, t-u, \tau))]dG(u) \\
&+ s_1 \int_t^{t+\tau} [ph^2(G_2(1, s_2, t+\tau-u)) + qh(G_2(1, s_2, t+\tau-u))]dG(u)
\end{aligned}$$

$$E[Z_2(t)Z_2(t+\tau)] \sim n_2^2 A e^{2\alpha t + \alpha \tau}$$

Define

$$D(s_1, s_2, t, \tau) = \sum_{k \geq j \geq 0}^{\infty} P[N_1(t)=j; N_1(t+\tau)=k] s_1^j s_2^k$$

$$\begin{aligned} D(s_1, s_2, t, \tau) &= 1-G(t+\tau) + \int_0^t [ph^2(D(s_1, s_2, t-u, \tau)) \\ &\quad + qb(s_1 s_2)h(D(s_1, s_2, t-u, \tau))] dG(u) \\ &\quad + \int_t^{t+\tau} [qb(s_2)h(D(s_2, 1, t+\tau-u, 0)) + ph^2(D(s_2, 1, t+\tau-u, 0))] dG(u) \end{aligned}$$

$$E[N_1(t)N_1(t+\tau)] \sim n_{01}^2 A e^{2\alpha t + \alpha \tau}.$$

Define

$$H(s_1, s_2, t, \tau) = \sum_{k \geq j \geq 1}^{\infty} P[N_2(t)=j; N_2(t+\tau)=k] s_1^j s_2^k$$

$$\begin{aligned} H(s_1, s_2, t, \tau) &= s_1 s_2 [1-G(t+\tau) + \int_0^t [ph^2(H(s_1, s_2, t-u, \tau)) + qh(H(s_1, s_2, t-u, \tau))] dG(u) \\ &\quad + \int_t^{t+\tau} [ph^2(H(s_2, 1, t+\tau-u, 0)) + qh(H(s_2, 1, t+\tau-u, 0))] dG(u) \end{aligned}$$

$$E[N_2(t)N_2(t+\tau)] \sim n_{02}^2 A e^{2\alpha t + \alpha \tau}$$

These results suffice to show that

$$E[W_1(t) - W_1(t+\tau)]^2 \rightarrow 0 \quad i=1, 2$$

$$E[W_{01}(t) - W_{01}(t+\tau)]^2 \rightarrow 0 \quad i=1, 2$$

so that $W_1(t) \rightarrow W_1$ and $W_{01}(t) \rightarrow W_{01}$, $i=1, 2$, in quadratic mean.

The results also yield that the limiting pairwise correlations among $W_1(t)$, $W_2(t)$, $W_{01}(t)$, and $W_{02}(t)$ approach 1 as $t \rightarrow \infty$, since we have

Lemma.

$$A-1 = \frac{[h''(1)[1+p] + 2pm^2]c}{1-m(p+1)c} \quad -1 > 0$$

where

$$c \equiv \int_0^\infty e^{-2\alpha u} dG(u) \quad .$$

Proof.

$$c > \left[\int_0^\infty e^{-\alpha u} dG(u) \right]^2 = \left[\frac{1}{m(p+1)} \right]^2 \quad .$$

It suffices to show

$$[h''(1)[1+p] + 2pm^2 + m(p+1)] \left[\frac{1}{m(p+1)} \right]^2 - 1 > 0$$

or

$$h''(1) + m > m^2 \left(\frac{p^2+1}{p+1} \right)$$

but

$$h''(1) + m > m^2 > m^2 \left(\frac{p^2+1}{p+1} \right) \quad .$$

Since

$$E[W_i] = E[W_{0i}] = 1 \quad i=1,2$$

and

$$E[W_i^2] = E[W_{0i}^2] = A \quad i=1,2$$

it follows that

$$W_1 = W_2 = W_{01} = W_{02} \quad \text{a.e.}$$

APPENDIX

Lemma 1. Consider the equation

$$K(t) = f(t) + m \int_0^t K(t-u) dG(u)$$

G is a distribution function on $(0, \infty)$, $G(0) = 0$, G is not a lattice distribution, f is a known function bounded on every finite interval, $m > 1$. Define $\alpha > 0$:

$$\int_0^\infty e^{-\alpha u} dG(u) = \frac{1}{m}.$$

Suppose $f(t)e^{-\alpha t} \rightarrow 0$ as $t \rightarrow \infty$, and $f(t)e^{-\alpha t}$ is bounded and integrable in $(0, \infty)$, then

$$K(t) \sim \left[\frac{\int_0^\infty f(u) e^{-\alpha u} du}{m \int_0^\infty u e^{-\alpha u} dG(u)} \right] e^{\alpha t}$$

Lemma 2. In the equation

$$K(t) = f(t) + m \int_0^t K(t-u) dG(u)$$

Suppose $m < 1$, and G is a distribution function, $G(0) = 0$. G may or may not be a lattice distribution. If

$$\lim_{t \rightarrow \infty} f(t) = c,$$

then

$$K(t) \rightarrow \frac{c}{1-m} \text{ as } t \rightarrow \infty.$$

These lemmas are from [3], Ch. 6, appendix.

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